PARENTAL DECISION MAKING FOR FRAGILE X SYNDROME CLINICAL TRIALS

by
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ABSTRACT

Background: There is a paucity of research evaluating parental proxy decision making for pediatric clinical trial participation. Fragile X Syndrome (FXS) is a rare genetic condition involving intellectual disability as its main symptom. Clinical trials have been offered and are under development. As intellectual disability directly affects an individual's personality, perceptions about trial participation and the potential for a disease-modifying therapy is likely different from the perceptions of parents raising a child with a physical disability or illness.

Objective: To improve understanding of parental proxy decision making for clinical trial participation of children with intellectual disability.

Methods: Interviews were conducted with parents from two groups: those who chose to 1) enroll their child with FXS in a trial; and 2) decline trial participation for their child with FXS. Parents were recruited through support groups. Interviews were transcribed and coded using thematic analysis.

Results: The most prevalent contextual decisional factor was attitudes about FXS medications. The most frequent trial-specific decisional factors were parental perceptions of the mechanism of the experimental drug, barriers and risks, and the match between parentally perceived purpose of the trial and their child's specific symptomatology. Parents' decision making processes involved weighing the risks and benefits of participation. Many parents reported making trial decisions primarily alone or with the support of their partner. All parents reported low decisional regret, though decisional conflict was found to range from low to high.

Conclusions: The most prevalent, primary decisional factors synthesized by parents within their decision-making process were their strongly negative or positive attitudes towards medicating their child's FXS symptoms, excessive travel to trial site and high number of required appointments, and perceived risk of physical side effects. Potential for direct individual benefit from participation most directly shaped parents' trial expectations and hopes, providing ultimate motivation for participation and resulting in high therapeutic optimism amongst parents who elected trial participation. Our results offer insight into potential targets of downstream research evaluating interventions to facilitate these decisions and reduce undesirable decisional outcomes.

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INTRODUCTION

There is a paucity of research evaluating parental decision making for pediatric clinical trial participation. These are high stakes decisions that may impact parent and child well-being (physical and psychosocial), as well as the effectiveness of the drug development process that is integral to the improvement of medical care. Due to the inherent lack of data supporting a novel experimental drugs' efficacy or safety, decisions to participate in clinical trials should be preference-based rather than prescribed or recommended by the health care community. Because there are concerns that parental decisions may not always be fully deliberated (Chang, 2008; Snethen et al., 2006), investigation of parental decision-making can help to inform efforts to improve this process. This study aimed to improve understanding of parental decision making for clinical trial participation of children with intellectual disability. Specifically, it focused on parent experiences of clinical trials for Fragile X Syndrome using semi-structured interviews.

Fragile X Syndrome (FXS) is an inherited genetic condition involving changes to the FMR1 gene located on the X chromosome. Such changes are estimated to occur as often as 1 in 2500 individuals (Hagerman, 2008). Its symptoms include cognitive impairment (ranging from mild learning disability to significant intellectual disability) behavior problems (such as inattention and hyperactivity), and less frequently, autism spectrum disorders (Bailey et al., 2008). Overall, FXS is the most common inherited cause of intellectual disability and the most common single-gene cause of autism (Belmonte & Bourgeron, 2006). Cognitive and social impairments are almost universally

seen in affected males and are commonly observed in affected females (Wheeler et al., 2013).

Clinical Trials

Clinical trials are essential for drug development. There are four stages of studies of therapeutic clinical trials. First, phase 1 trials include healthy volunteers, or especially in the case of rare disorders, people with the disease or condition in question. Phase 1 trials aim to elucidate drug safety, side effects, and appropriate dosage. Approximately 70% of drugs complete phase 1 study to enter phase 2, which provides data on efficacy and side effects of the drug in development. About 33% of drugs in phase 2 will move to phase 3, in which expanded studies enable further research into the efficacy and monitoring of adverse reactions. After moving through the stages of clinical trials the FDA examines data from clinical and preclinical studies to either approve or not approve the drug's marketing. Approximately 25-30% of novel drugs in phase 3 clinical trials are approved for marketing and move to phase four, in which the FDA follows the drug and monitors its post-market safety and efficacy (FDA, 2015).

In some cases, the process described above is modified for trials for rare disorders. Clinical trials have particular importance in the rare disease community, where advances in drug development have lagged behind more common diseases, target populations are significantly smaller, and funding is often more difficult to ascertain.

Decisions about Participation in Clinical Trials: Pediatrics

Most research on decision making for clinical trials examines adults making decisions about their own participation (Ferrer et al., 2016; Abhyankar et al., 2016;

Wenzel et al., 2015). In pediatrics, the majority of data on parental clinical trial decision-making comes from the pediatric oncology context. An analysis of 22 qualitative studies of decision making for pediatric oncology trials deemed it difficult to achieve informed consent due to complex research protocols, as well as parents' emotional distress and dependence on the consenting physician. Parents have frequently and inaccurately attributed therapeutic intent to research participation. They desire to act in the best interest of their child, and in this context have reported fearing they made the 'wrong decision' about trial participation (deVries et al., 2011).

A literature review of parental decision making about care and treatment (including, but not limited to clinical trial participation) for children with cancer reveals that child's quality of life/wellbeing, parental hope/expectations, support/supportive care, communication, and information were important themes in considering these decisions (Markward et al., 2013).

A recent qualitative study evaluated parent and clinician motivations and expectations for involvement in clinical trials for the rare pediatric disorder Duchenne muscular dystrophy (Peay et al., 2014). High trial expectations of direct benefit were reported by parents and many clinicians, however many parents were able to differentiate expectations from hope for a cure. Parental expectations manifest from the views of other parents, advocacy organizations, and trial sponsors. Parents' primary motivation for enrolling was the potential for benefit, and the decision was described as easy or a 'non-decision.' They did not perceive clinicians to have a significant role in their decision-making. It is unknown whether these findings represent experiences of other parents making decisions about enrolling their child in a rare disease clinical trial.

Therapeutic misconception, or the belief that the purpose of a clinical trial is to benefit the individual patient rather than gather data to develop scientific knowledge, is a particular bioethical concern for decision-making in clinical trials. Therapeutic misconception has been identified as a potential issue within pediatric as well as adult contexts (Peay et al., 2014; Jansen et al., 2011). Some researchers have emphasized the idea that therapeutic misconception may be a mislabeling. This argument posits that what is labeled as therapeutic misconception may actually be a situation in which a parent is hoping that his/her child will receive a treatment that is later shown to be better than the standard treatment, and that this is the purpose of clinical trials (Shilling & Young, 2009). Nevertheless, unrealistic situational optimism surrounding clinical trials raises concern as a potential threat to informed decision-making and source of exploitation of research participants (Jansen et al., 2011).

A study evaluating perceived benefits and barriers to pediatric clinical trials suggests potential benefit of drug, perceived harm due to mistrust of researchers, and logistics to be primary factors in decision-making about clinical trials in pediatrics (Barakat et al., 2013). Another survey of 261 parents of healthy children, and parents of children ill with conditions including diabetes, asthma, cystic fibrosis, phenylketonuria, and gastroesophageal reflux disease, myopathy, and encephalopathy, identified "direct benefits for their child" as the main factor motivating participation in pediatric clinical research (Vanhelst, 2013).

Specific for clinical trials in FXS, the degree to which adult affected individuals are believed to be able to consent for trials has been investigated. A recent study determined that parents of 29% of affected males reported that their adult son was not at

all capable of participating in the decision to participate in the trial, yet a majority of affected individuals were perceived to be able to participate at some level in the consent or assent process (Bailey et al., 2014).

No study has yet examined parental decision-making for enrollment of children with intellectual disability in a clinical trial of drug development. It is not clear how parental clinical trial decision-making may be different in the context of a primarily cognitive condition rather than a primarily physical condition. Having a richer understanding of this decision within this context could help inform future quantitative studies that aim to examine ways of improving facilitation of these decisions for parents.

Parenting a Child with Intellectual or Developmental Disability

Most pediatric clinical trial research has been conducted on drugs for diseases with primarily physical symptoms (such as cancer and Duchenne muscular dystrophy). In considering trials for FXS, it is first important to contextualize this research in what is known about raising a child afflicted by a condition with primarily cognitive symptoms. Because intellectual disability is relatively common, with between 1 in 50 and 1 in 20 families with affected children worldwide, there is data describing the experience of raising a child with intellectual disability or developmental delay. In the vast majority of cases, parents and other family members care for children with intellectual disabilities directly (Families Special Interest Research Group of IASSIDD, 2014).

Parental Psychological Wellbeing

While mothers of children with intellectual disabilities report greater parenting demands, increased stress levels, and poorer physical and psychological health than parents of non-disabled children, most studies have demonstrated the majority of mothers

of children with intellectual disability (ID) report normative levels of well-being (Olsson & Hwang 2001; Saloviita et al., 2003; Blacher et al., 2005; Singer 2006; Gerstein et al., 2009; Miodrag & Hodapp 2010; Glidden & Schoolcraft 2003; Baker et al., 2005; Glidden & Jobe 2006; Olsson et al., 2008). There is less known about fathers' well-being; however, some research suggests that the association between parenting a child with ID and lower well-being is even less pronounced among fathers than mothers, who generally report psychological well-being. Fathers similarly report lower levels of psychological distress than mothers (Olsson & Hwang 2001; Salvoiita et al., 2003; Gerstein et al. 2009; Emerson et al. 2010; MacDonald & Hastings 2010).

Factors Associated with Variation in Parental Psychological Wellbeing

Parental well-being appears to be highly dependent upon the affected child's degree of maladaptive behavior. Child behavior problems, rather than ID *per se*, can be associated with lower levels of parental wellbeing (Glidden 2012; Nalavany et al., 2009; Totsika et al. 2011a,b). Research comparing parental wellbeing among behavioral phenotypes has found that the association between child ID and parental well-being is significantly less pronounced among parents of children with Down syndrome than among parents of children with other diagnoses, particularly autism. Researchers have hypothesized that this is related to a higher level of adaptive behavior amongst individuals with Down syndrome and the higher prevalence of behavior problems among children with autism (Esbensen et al., 2010; Abbeduto et al., 2004).

Parents are described as using a variety of coping strategies, such as positive reframing, and have been identified to harbor optimism and experience hope (Hastings & Taunt 2002; Kausar et al., 2003; Baker et al. 2005; MacDonald et al., 2010). There is

limited research on the effect of personality and coping strategies in upholding well-being (Families Special Interest Research Group of IASSIDD, 2014). Because clinical trial participation is likely influenced by parental coping, improving understanding of the trial participation decision-making process may help further elucidate the role of coping in selecting to participate in a clinical trial and the impact of these trials on parent and child well-being.

Parenting a child with Fragile X Syndrome

There is also a body of literature specific to the ways parents experience raising a child with FXS. Fragile X Syndrome is relatively unique compared to several other common ID conditions due to its single gene cause and variation in phenotype. The main impact that this may have on parental coping and well-being is the increased likelihood for families to have multiple affected members, who may express different degrees and manifestations of outcomes. Additionally, maternal guilt over transmitting a mutation in the FMR1 gene may affect psychological coping and reactions to parenting a child with FXS (James, 2003).

Parents of adolescents and young adults with FXS have been observed to fare better (in terms of depressive symptoms and pessimism) than parents of adolescents and young adults with autism spectrum disorder (ASD) but worse than fathers of adolescents and young adults with Down syndrome (Hartley et al., 2012; Abbeduto et al., 2004). Additional comparisons among FXS and other conditions have suggested that parenting involves more challenges to maternal psychological well-being than Down syndrome and the combination of FXS and autism is considered to be especially challenging. More specifically, mothers of children with FXS reported more conflict within the family and

more pessimism about their son's future compared to mothers of sons with Down syndrome. Additionally, mothers of sons with FXS and comorbid ASD were found to have lower levels of reciprocated closeness with their son than mothers of sons with other conditions (Lewis et al., 2006). Families affected by FXS have been observed to report a high quality of life but particularly struggle with a lack of social support, social life, and parenting knowledge (Raspa et al., 2014).

Behavior problems and mood instability have been suggested as the most debilitating aspects of FXS. Examples of challenging behaviors common amongst affected children are tactile defensiveness, hand flapping, poor eye contact, hyperactivity, tantrums, perseveration, hyperarousal to sensory stimuli, impulsivity, self-injury, and aggression (Hatton et al., 2002; Hagerman et al., 2009; Symons et al., 2010).

Fragile X Syndrome Clinical Trials

The past ten years have marked major progress in designing treatments for FXS. In the past, gold-standard medical management involves symptom management rather than curative therapeutics. The state of the research began to change after the mGluR theory of FXS was presented in 2004, raising the possibility of alternate treatment options. The theory postulates that the neurological deficits in individuals with FXS are due mainly to downstream consequences of overstimulation of the mGluR pathway (Bear et al., 2004).

The mGlurR theory has become the basis of several targeted experimental treatments for FXS, such as use of the mGluR5 antagonist AFQ056 (mavoglurant, Novartis Pharmaceuticals). In addition to the mGluR system, the GABA system has been implicated in the cognitive impairment, anxiety, and autism symptoms of FXS as well as

other neuropsychiatric and neurodevelopmental disorders. Other experimental medications for FXS have targeted this system. Included in this category of drugs are arbaclofen (Seaside Therapeutics) and ganaxolone (Marinus Pharmaceuticals) (Lozano et al., 2014). Clinical trials evaluating the effectiveness of these drugs have been ongoing for approximately eight years (Gomez-Mancilla et al., 2014). Because behavior problems are often the most significant concern reported by parents, ongoing clinical trials evaluating the efficacy of novel FXS drugs are targeting reduction in behavior problems (Sansone et al., 2012).

For many FXS drug development trials, approximately 30% of participants respond well to the experimental drug. This may not be adequate to demonstrate overall efficacy and result in FDA approval for marketing. Currently, researchers are attempting to identify biomarkers (such as FMR1 gene methylation) for predicting efficacy of particular drugs for specific individuals (Lozano et al., 2014).

Another barrier to trial success has been the reliance on family questionnaires related to the affected individual's behavior as the outcome measure. This outcome measure raises concern of placebo effect, and researchers are aiming to discover more quantitative outcome measures that relate to central nervous system function or molecular changes. Additionally, the process of obtaining FDA approval for medications sometimes requires companies to establish safety and efficacy in adults before studying a given drug in children. It is speculated that reversing behavioral and intellectual abilities in FXS is more difficult in adults than children, and so low efficacy of adult studies prevents the experimental drugs from reaching younger age groups (Lozano et al., 2014).

While the advent of drug-development clinical trials has likely been a welcome development in the FXS community, the difficulties inherent in the process may have implications for parents' expectations, hopes, and motivations. Little is known about how parents and children respond to these trials. Research has not yet addressed the emotional and physical toll of participation.

Theoretical and Conceptual Framework

Our research aimed to explore parental decision-making, motivations, and the overall experience with FXS clinical trial participation. These concepts were explored using the Common Sense Model (Diefenbach and Leventhal, 1996), Epstein and Street's adaptation of Charles et al.'s Model of Treatment Decision Making (2007), and Hoberman et al.'s conceptual model of Factors that Influence Parental Decisions to Participate in Clinical Research (2013).

Common Sense Model of Illness Representation

First, Leventhal's Common Sense Model of Illness Representation (Diefenbach & Leventhal, 1996) was used to inform the stress and coping context of the experience that will be studied. The model takes a self-regulatory approach for studying and understanding health behaviors, such as treatment decisions or clinical trial participation. It provides a model for conceptualizing stress and coping in the face of health threats, and thus can be used to contextualize stress and coping experienced by parents and how that may be affected by clinical trial participation. Our study proposed that clinical trial participation may be one way that parents cope with raising a child with FXS. The model posits that individuals are active problem solvers who perceive the reality of health threats and have emotional and cognitive reactions to the threat. The three central tenets

of the model are: 1) individuals are active problem solvers both seeking information and acting to test hypotheses about the meaning of his or her somatic sensations and physical condition 2) the illness representation is the central cognitive construct that guides coping and the appraisal of action outcomes; 3) representations are highly individualized and may not be in accord with medical facts (Deifenbach & Leventhal, 1996). This study explored parents' experiences of raising their child with FXS using this stress and coping model as a framework. The interview prompted parents to explore how their experiences of parenting their child affected their decision-making. Also, the interviews explored the effect of their decision to participate (or possibly participate) on their parenting experience.

Treatment Decision Making Model

Second, our conceptualization of parental clinical trial decision-making was informed by Charles and colleagues' Treatment Decision-Making Model. This model describes a spectrum of decision-types from paternalistic (clinician decides treatment) to shared (clinician and patient together decide treatment), and then informed (patient decides treatment based on information from the clinician and other sources). According to this model, each type of decision-making proceeds through three stages, information exchange, deliberation, and making the final decision (Charles et al., 1999). Epstein and Street claim that ideally, even in unilaterally-made final decisions, the decision-making process itself should be characterized by active engagement by all parties in the information-exchange and deliberation stages. It also argues that the quality of the patient-clinician interaction, not the patient's role *per se* in deciding treatment, is the most important factor affecting the quality of decision-making (Epstein & Street, 2007).

This model assists our research as it outlines different types of treatment decisions and frames the decision- making process that will be explored. Specifically, the model guided us to explore the role of the health care provider in the decision-making process as well as the impact of the decision-making process on the relationship with the healthcare provider.

Factors that Influence Parental Decisions to Participate in Clinical Research

Finally, Hoberman and colleagues (2013) have created a model of factors that influence *parental* decisions to participate in clinical research based on prior research, which was used to inform the querying of such factors in our interview guide. The model suggests child characteristics, parental characteristics, and study characteristics to all together lead to parental understanding. Parental understanding is then suggested to lead to parental perceptions of the study, which is then suggested to lead to decision-making. Decision-making is considered to be modifiable by external factors, and finally, decision-making is considered to lead to the decision to participate or not participate in clinical research (Hoberman et al., 2013).

SPECIFIC AIMS

The objectives of this research were to improve understanding of parental proxy decision making for clinical trial participation of children with Fragile X and explore parent experiences of drug development clinical trials for Fragile X Syndrome.

Aim 1: To describe the decision-making process about participating in these trials. In particular, we aim to capture parents' preferences, motivations, influencing factors, and barriers related to trial involvement.

Aim 2: To describe parental decisional conflict or decisional regret related to their decision-making for clinical trial participation.

METHODS

Study Design

This study was carried out using a qualitative design with semi-structured interviewing followed by inductive coding as themes emerged. The qualitative approach was selected because little was known about parental proxy decision-making for FXS trials, or even the perceptions of drug trials amongst parents with children who have intellectual disability.

The study aimed to explore the decision-making processes of parents of individuals with FXS surrounding therapeutic trial participation. Parents who had a child enrolled in a trial in the past (Group 1), and parents who have denied trial participation (Group 2) were interviewed.

Recruitment and Procedure

Parents were recruited from the National Fragile X Foundation (NFXF), which has over 1000 members, via website post and in-person recruiting at the NFXF 2016 conference, and through FRAXA twitter and e-mail list-serv. Website posts and e-mail messages consisted of the recruitment letter, which is included in Appendix A. Online outreach was supplemented with a link to the study's NHGRI website page. The content of online outreach is included in Appendix B. Parents recruited through NFXF and FRAXA internet outreach were provided with the e-mail contact information of the interviewer. Upon being contacted by interested parents, the interviewer scheduled a time to call each interested and eligible participant. All participant contact information (first name, email address, and phone number only) was kept in a confidential database, and was destroyed after completion of each interview. In-person recruitment at the NFXF

conference utilized word-of-mouth and direct conversations with parents about the study, as well as placement of flyers around the conference center. The flyer layout is included in Appendix C. Parents recruited at the conference were interviewed in person when schedules permitted. Parents were also able to leave their contact information with the interviewer (CDA) if they preferred to participate in a phone interview after the conference.

At the appointed time, the parents participated in a phone-based or in-person informed consent process (see Appendix D). Once the participant verbally consented to participate in the study, the interviewer proceeded with the interview, following a semi-structured interview guide. The participant was able to request to be withdrawn from the study at any time up until participant identifiers were destroyed. Audiotapes of the interviews were transcribed by an external agency and were coded by the primary investigator (CDA) for thematic analysis. A second coder coded 30% of the interview data to assess inter-rater reliability.

Study Sample

Parents needed to meet these criteria in order to participate in the study: 1) be a parent of a person (of any age) with FXS, 2) be 18 years of age or older, cognitively intact, and able to speak English, 3) have experience either with choosing to enroll their child in a drug development clinical trial for FXS in the past or declining an offer of drug development clinical trial participation for their child with FXS. One parent was recruited from each eligible family.

Data Collection

Interviews were conducted over the phone and in-person depending on the participant's preference and availability. In this study, 17 interviews were conducted in-person and 17 interviews were conducted over the phone. For both in-person and phone interviews, parents were given a copy of the informed consent information to review on their own (via e-mail for phone participants, and in hard-copy for in-person participants), and the primary investigator reviewed its content with them prior to the interview. Informed consent to proceed with the interview was provided verbally by all participating parents. Each interview was audio-recorded and uploaded to a password-protected website. The recordings were transcribed verbatim and checked by the interviewer (CDA) for accuracy. The semi-structured interview was first guided by sociodemographic questions (see Appendix E) and then by open-ended questions (see Appendix F) and took between 30 and 60 minutes, with an average of about 45 minutes. Following each interview, the interviewer (CDA) completed the interview summary form (see Appendix G) to capture initial reflections.

Data Analysis

Coding

The interviews were coded to identify common and interrelated themes supported by a software program, NVIVO. A set of preliminary codes based on *a priori* topics was applied to several initial transcripts, and concurrently, a set of emerging codes was identified and included in the codebook. Codes continued to be added until no text was identified that could not be coded using the established codes. Interviews were coded concurrently with data collection and early interviews were re-coded using the final expanded codebook.

An initial codebook including the following preliminary themes was refined throughout coding the initial transcripts: expectations, motivations, and hopes of parents related to trial participation, parent decision-making type (i.e. shared, informed, paternalistic, as framed by Charles et al. 1999), parent decision-making influencing factors (informed by Hoberman et al., 2013), parent decision-making barriers, and parental regret or satisfaction level with the decision they made or with their decision making experience. The final codebook is included in Appendices H through K.

A second coder coded ten randomly selected interview transcripts, representing about 30% of the total data, to establish reliability. An inter-rater-reliability Kappa score, calculated based off of ~10% of the total data (3 of the 10 second-coded interviews), yielded 0.85 suggesting good reliability of the coding.

Thematic Analysis

Coded findings were interpreted via thematic analysis. This approach identifies common themes and explores each theme in detail. Transcribed data was read and reread to promote overall familiarity. Codes were collated into potential themes, and all data relevant to each potential theme was gathered. Potential themes were reviewed in relation to coded extracts and the entire data set. Clear definitions and names for each theme were developed to refine the specifics and the overall narrative. The selection of vivid, compelling illustrative quotes and final analysis of these extracts enabled relation back to the research question and literature in the final stage of analysis. Finally, this process generated the results, which are described using conceptual systems and an overarching narrative (Vaismoradi et al., 2013). Socio-demographic data was collected to enable

analysis of variation between subgroups once saturation was reached within given subgroups.

RESULTS

Sample Characteristics

Thirty-four parents participated in the study. Sixteen of the participating parents were interviewed about their experience with choosing to have their child enrolled in drug development clinical trials in the past (Group 1), fifteen of the participating parents were interviewed about their experience with declining drug development clinical trials (Group 2), and three parents who were deliberating the possibility of future clinical trial participation for their child and did not meet the criteria for either of the two groups were also interviewed. Tables 1 and 2 describe the socio-demographic and relevant medical characteristics of the participants in Groups 1 and 2 respectively. The majority of participants were female, married, and white. All of the parent participants were the biological parent of the affected child except for one adoptive mother. Some parents had more than 1 child with FXS, and were guided to focus on one affected child for whom they have considered trial participation for the interview. The participating parents' children ranged in age from 20 months to 32 years old, and ranged in severity of FXS symptoms from mildly affected to severely affected by parent report.

Parents in Group 1 had experience participating in several trials, including Seaside STX209 or Arbaclofen, Novartis AFX056, UC Davis Sertraline, UC Davis Minocycline, Roche RO4917523, UC Davis/Marinus Ganaxolone, Alcobra MG01C1, and Neuren NNZ-2566. Six parents in Group 2 had experience declining specific trials, including Seaside STX209 or Arbaclofen, UC Davis Sertraline, and Alcobra MG01C1. Nine parents in Group 2 had experience declining several trials generally and did not recall the specific trials they had declined.

Table 1. Sample Characteristics, Group 1, (n=16)

Sociodemographic characteristics		**n (%)**
Sex	Male Female	3 (19) 13 (81)
Parenting Relationship	Biological Adoptive	16 (100) 0 (0)
Biological Mother Carrier Status	Pre-mutation (≤ 200 repeats) Untested or unknown Full mutation (>200 repeats)	12 (92) 1 (8) 0 (0)
Education	*Highest Degree Completed* High School Degree Associates or Bachelors Degree Graduate/Advanced Degree	 1 (6) 9 (56) 6 (38)
Marital Status	Married Not Married	12 (75) 4 (25)
Race	White or Caucasian, Non-Hispanic Black or African American Other	13 (81) 3 (19) 0 (0)
Total Number of Children in Family	2 or more children	13 (81)
Number of Children affected by FXS in Family	2 or more children with FXS	4 (25)
Affected Child FXS Symptomatology	*By Parent Self-Report* 'Mildly affected' 'Moderately affected' 'Severely affected' 'Co-morbid autism' 'Co-morbid seizures'	 5 (31) 6 (34) 4 (25) 3 (19) 2 (13)
Affected Child Age At Time of Interview	Child (0-13 years) Adolescent (13 years-18 years) Adult (≥18 years)	6 (38) 5 (31) 5 (31)
Affected Child Age At Time of Trial Participation	Child (0-13 years) Adolescent (13 years-18 years) Adult (≥18 years)	10 (62) 3 (19) 3 (19)

Table 2. Sample Characteristics, Group 2, (n=15)

Sociodemographic characteristics		**n (%)**
Sex	Male Female	2 (13) 13 (87)
Parenting Relationship	Biological Mother or Father Adoptive Mother	14 (93) 1 (7)
Biological Mother Carrier Status	Pre-mutation (≤ 200 repeats) Untested or unknown Full mutation (>200 repeats)	8 (67) 4 (33) 0 (0)
Education	*Highest Degree Completed* High School Degree Associates or Bachelors Degree Graduate/Advanced Degree	 1 (7) 8 (53) 6 (40)
Marital Status	Married Not Married	13 (87) 2 (13)
Race	White or Caucasian, Non-Hispanic Black or African American Other	13 (86) 1 (7) 1 (7)
Total Number of Children in Family	2 or more children	12 (80)
Number of Children with FXS in Family	2 or more children with FXS	3 (20)
Affected Child FXS Symptomatology	*By Parent Self-Report* 'Mildly affected' 'Moderately affected' 'Severely affected' 'Co-morbid autism' 'Co-morbid seizures'	 5 (33) 6 (40) 4 (27) 8 (53) 1 (7)
Affected Child Age At Time of Interview	Child (0-13 years) Adolescent (13 years-18 years) Adult (≥18 years)	3 (20) 3 (20) 9 (60)
Affected Child Age At Time of Trial Decline	Child (0-13 years) Adolescent (13 years-18 years) Adult (≥18 years)	5 (33) 5 (33) 5 (33)

Table 3. Sample Characteristics, Interviewees in neither group, (n=3)

Sociodemographic characteristics		**n (%)**
Sex	Male Female	1 (33) 2 (67)
Parenting Relationship	Biological Adoptive	3 (100) 0 (7)
Biological Mother Carrier Status	Pre-mutation (≤ 200 repeats) Untested or unknown Full mutation (>200 repeats)	2 (100) 0 (0) 0 (0)
Education	*Highest Degree Completed* High School Degree Associates or Bachelors Degree Graduate/Advanced Degree	 0 (0) 1 (33) 2 (67)
Marital Status	Married Not Married	3 (100) 0 (0)
Race	White or Caucasian, Non-Hispanic Black or African American Other	3 (100) 0 (0) 0 (0)
Total Number of Children in Family	2 or more children	3 (100)
Number of Children with FXS in Family	2 or more children with FXS	1 (33)
Affected Child FXS Symptomatology	*By Parent Self-Report* 'Mildly affected' 'Moderately affected' 'Severely affected' 'Co-morbid autism' 'Co-morbid seizures'	 1 (33) 1 (33) 1 (33) 1 (33) 1 (33)
Affected Child Age At Time of Interview	Child (0-13 years) Adolescent (13 years-18 years) Adult (≥18 years)	2 (67) 0 (20) 1 (60)

Our interviews uncovered five major themes; motivations, contextual decisional factors, trial-specific decisional factors, decision making process, and decisional conflict and regret.

Motivations Behind Choice to Participate or Decline

Parents were asked to reflect upon what ultimately motivated them to either decline or elect participation in a drug development clinical trial. Parents in Group 1, who had chosen to enroll their child in a drug development trial for FXS, described two major motivations to elect participation. Some were motivated only by their belief that by electing participation they were giving their child opportunities to reduce troubling

symptoms (Group 1 n=5). Others were motivated by this chance of individual benefit as well as altruism in benefitting the entire FXS community (Group 1 n=11).

> *I was motivated by those possibilities that he could sit in his classroom and learn to read, and just pay attention to what was going on. Because I think if he was able to sit still long enough, he could get so much more. Because he gets a lot now, just in passing. If he was able to actually sit through an instruction, it would just be amazing. (Mother 015, Group 1)*
> *Again, really just what motivated me was the potential outcome. And, honestly, even knowing that if he got a placebo, just the fact that, by and large, this study could obviously help the whole Fragile X community. So I also was realistic knowing that even if he got a placebo, that even by participating, we were still kind of giving back. Moving the science forward. (Mother 033, Group 1)*

Parents in Group 2, who had declined trial participation for their child with FXS, mentioned a range of motivations to decline, including poor match between trial outcome and their child's particular symptomatology (Group 2 n=5), logistical inconveniences (travel, scheduling, or number of appointments) (Group 2 n=5), blood draw requirements (Group 2 n=2), inability for their child to remain on their regular medications throughout the trial (Group 2 n=3), low perceived likelihood of long-term access to the experimental drug (Group 2 n=3), general attitudes against medicating their child for FXS symptoms (Group 2 n=4), and concern around the risks of the trials (Group 2 n=3).

> *Ultimately I've become very particular about the outcome and if the outcome they are measuring is not a high priority for us then I decline them. It has to be related to what is very important to us. (Mother 028, Group 2)*
> *I was motivated to decline ultimately because of travel. And number of visits. I guess, it would come down to those two items. (Mother 031, Group 2)*

Table 4: Group 2 Major Reasons for Declining

Participant ID Number	Major Reasons for Declining
001	Blood draw requirements, inability for child to remain on regular medications throughout trial, and low perceived likelihood of long-term access to the experimental drug
002	Poor match between trial outcomes and particular child symptomatology
003	Blood draw requirements and inability for child to remain on regular medications throughout trial
005	Excessive travel to trial site and high number of required visits
007	General attitudes against medicating child's FXS symptoms, excessive travel to trial site and high number of required visits, and low perceived likelihood of long-term access to the experimental drug
008	Excessive travel to trial site
009	Concern around risks and safety
014	Concern around risks and safety, general attitudes against medicating child's FXS symptoms
016	Difficulty in scheduling trial-related appointments
018	Inability for child to remain on regular medications throughout trial
024	General attitudes against medicating child's FXS symptoms
025	General attitudes against medicating child's FXS symptoms, concern around risks and safety, poor match between trial outcomes and particular child symptomatology
026	Poor match between trial outcomes and particular child symptomatology and low perceived likelihood of long term access to the experimental drug
028	Poor match between trial outcomes and particular child symptomatology
031	Excessive travel to trial site

Contextual Factors Impacting Decision Making

Several background contextual factors specific to the participating parents, their parenting experience, and their child were reported as influencing the parents' decision making about clinical trial participation. Most frequently, parents reflected on their attitudes toward medication and research, the juxtaposition of FXS and

conceptualizations of their child's personality, and the fit between clinical trial participation and their child's particular symptomatology and age.

Attitudes about Medications to Treat Symptoms of FXS

General attitudes toward medication use to treat symptoms of FXS were reported by parents as shaping their attitudes about participation in clinical trials (n=21). Parents of children with FXS held a range of attitudes about medicating their child. Some decliners shared only negative past experiences with medications and skepticism around medicating their child for FXS symptoms (Group 1 n=0, Group 2 n=5).

> *Because he was developing and still growing, I did not want medication to interfere with that development. That he needed to learn how to live in his own body with who he was. (Mother 025, Group 2)*

Other parents only described medication use positively (Group 1 n=6, Group 2 n=2), sharing past experiences in which they believed medication improved their child's quality of life or was an integral component of caring for their child. One parent described medication as a tool to unlock the potential of children with FXS:

> *You know, with Fragile X, if you can just take care of the anxiety, the distractibility and certain things, then they're free to be able to be so much more, and that's the thing about the drugs. It just makes it possible for them to reach their potential and to be themselves, you know, and do things, and do the therapy they're in. (Mother 013, Group 1)*

Other parents described mixed views of medications—perceiving both negative and positive aspects (Group 1 n=3, Group 2 n=3). A subset of these parents described their first time choosing to medicate their child as being most challenging:

> *I wasn't even giving my son medicine. It took me a while before I said, 'Okay, you need to start medicating him.' So I fought that medicine and, 'No, you're not medicating my child,' for a very long time. So when I did, my doctor actually congratulated me and was like, "You're probably one of the first persons that waited until your child actually really, really needed the medicine and didn't just go and say, 'Okay, give my child some Ritalin.' (Mother 014, Group 2).*

Attitudes about Research

Parents described their general attitudes towards biomedical research with most parents (n=19) sharing positive opinions of research. Those who felt positively about research described participation as an opportunity to learn more about their child, FXS, and other related or co-morbid conditions. They also saw research participation as an opportunity to contribute to what is known about FXS in hopes of improving care and information quality for themselves as well as the community broadly.

> *I would hope that parents would get more involved, you know, because sometimes that will open up opportunities for you to participate and to contribute. And I do think participating in research will give you a better opportunity to understand the disorder and your child as well. (Mother 029, Group 1)*

The minority of parents (Group 1 n=1, Group 2 n=3) who shared apprehension about research was afraid of the notion of their child being used as a 'guinea pig' or a 'test subject,' coupled with the unknown risks of experimental drugs.

> *I was very scared about anything, any medicine, and putting her, feeling like she'd be a guinea pig with medicine. The medicine thing and side effects and what it could mean especially when people don't know. That's why they're testing it, and I really was repelled—actually, that's a strong word but resistant always for that for years. (Mother 013, Group 1)*

Symptomatology of Affected Child

Parents who perceived their child as mildly affected and those who thought of their child as severely affected incorporated the symptomatology of their child most into their consideration of drug development clinical trial participation. Parents of mildly affected children described more apprehension around trial participation than parents of severely affected children. They were concerned that experimental drugs would detrimentally affect their child's development and described feeling satisfied with therapies that were not drug based. At the same time, parents of reportedly mildly

affected children felt that their child could contribute to scientific knowledge about FXS, and that their child had a level of functionality that would make participation less burdensome compared to families with more severely affected children.

> *Considering the gains that we would make compared to the gains that a child that was extremely low functioning would make, in our minds the researchers would probably not suggest the trial for the benefit of our child (Father 007, Group 2)*
>
> *Because he was so high functioning there was great interest. It is a bit of a funny story with one of the researchers examining our son. We thought there was great interest to see how the trial would benefit a child that was already quite verbal just to see where it would take it on that level (Mother 002, Group 2)*
>
> *He's my little experiment. Because I want to help him, and because he will let them take blood. Because we started doing that when he was little. And because we were going there for blood since he was four years old, he is not one of those kids that you have to nudge and tousle to get blood from. (Mother 034, Group 1)*

Parents of severely affected children expressed interest in FXS medication development, but also described being more frequently ineligible for studies and less able to participate compared to parents of mildly affected children due to greater caretaking demands (Group 1 n=0, Group 2 n=2).

> *I think -- I believe, honestly, that most trials look at people who are more -- higher than on the lower end. Sometimes I feel like we're left out. But I feel like, too, you should be trying to help the lower-end ones more because they're the ones that's struggling and don't have the capability of doing certain things. (Mother 014, Group 2)*
>
> *Unfortunately, he is more affected than the vast majority of kids with Fragile X. It wouldn't have been fair, to my son, to put him through a trial. He already has enough issues navigating life and trying to stay sane. And honestly, the people who would've gone with him -- me, his dad, whomever, it wouldn't have been fair to us, either, to try and, you know, make ourselves go through that because it would've been ugly. (Mother 031, Group 2)*

Age of Affected Child

The age of the affected child appeared to play a role in a parents' deliberation of drug development clinical trial participation. Two parents of younger children expressed

more apprehension towards clinical trial participation due to anxiety surrounding the potential of an experimental medication to interfere with their child's development and have long-term negative ramifications (Group 1 n=0 Group 2 n=2).

> *They're growing and developing and here you're introducing these chemicals into their body and you don't know the impact on development. (Mother 024, Group 2)*

Parents also viewed the age of their child as affecting the likelihood that a successful targeted treatment for Fragile X Syndrome would be of benefit to their child. Most parents of older children shared pessimism that a targeted therapeutic would be effective for their child, and explained that such a medication would most likely be effective for affected infants and toddlers treated earlier in their development (Group 1 n=1, Group 2 n=3).

> *I don't think that a cure is going to come around with enough time for my son to benefit from it. I think it's more complex than it will take to fix in the next, even ten or fifteen years and I worry that as somebody with Fragile X gets older, when you start reversing that, what happens to them? I think the older you get, probably the more difficult it is to relearn or to readjust so I just don't see it happening in his lifetime. I see all these studies trying to impact young children and babies. I think finding a cure is critical, it absolutely has to be done but it's not going to affect my family to any great degree. (Mother 028, Group 2)*
>
> *Even if we were able to do gene replacement, and we popped in a new copy of the gene, his brain would probably have so much catching up to do with a typical developmental process that he probably would always have a little trouble functioning himself in the real world. He'll probably always be a little mentally impaired even if gene replacement were to land on our doorstep like today. You just kind of get set in your ways, get used to doing things a certain way, and your brain kind of forms around that, so it's not just this gene and just these proteins affected. You know, their whole brain is kind of formed around that way they learned it. (Mother 032, Group 1)*

Effects of FXS on Parental Conceptualization of Child's Personality

The majority of interviewed parents found many personality strengths to be the best or most beneficial aspects of their child's Fragile X Syndrome. The personality

strengths most commonly attributed to the syndrome were their child's ability to express love (Group 1 n=8, Group 2 n=3), overall happiness (Group 1 n=6, Group 2 n=5), kindness and compassion (Group 1 n=4 Group 2 n=6), and sense of humor (Group 1 n=4, Group 2 n=7).

> *Your life will be more enriched because of a person with Fragile X. You know, really get to know them. You know, laugh with them. They're really funny... Spend a little time each day viewing life through their eyes because they live in a pretty nice world. They see nice people. Everybody in their -- you know, for the most part, everyone they meet is nice. They don't see a mean person. (Mother 001, Group 2)*

Despite feeling these characteristics to be part of their child's FXS, most parents did not perceive these personality strengths to be threatened by a potential or existing experimental drug. When they considered how a hypothetical successful targeted treatment for FXS would change their child's life, nearly all interviewees in both groups explained that their child would become happier and more functional versions of themselves.

> *I think that if there were a drug that helped that would mean he would be able to learn more. That doesn't mean that he would turn on a dime and suddenly not be him. I think it would be just wonderful to help him explore the world. (Mother 003, Group 2).*
> *He would be able to communicate with us more. He would be able to communicate with other people who don't know him. He would- I think he would still be this fun-loving guy, but we would probably get more out of him and understand. I know what his wants and dislikes are, but he would be able to actually communicate to us, even if he couldn't talk and he was able to use a communication device better than what he is doing now, meaning that he could actually put a sentence together, that right there would be a milestone in itself. (Mother 014, Group 2)*

A small subset of parents (Group 1 n=0, Group 2 n=2) perceived that their son's FXS symptoms may benefit his existing quality of life, implying that a targeted therapeutic may reduce his quality of life if it was successful in treating his FXS.

> *It's hard to say what it would be for my son. Would it be unnatural? All of a sudden, he starts understanding things, he can make connections and grow, you know, as a person? I don't know, I couldn't because I don't live in his head.... Would it be a good thing for him to all of a sudden be able to see the world for its good and bad? I don't know. I mean, he's lived his whole life being looked after and living in his little world and he's happy most of the time. It's like one of those questions where a person who's lived their life deaf and wanted to know what it's like to hear and others don't.* (*Mother 005, Group 2)*

These interviewed parents described a theoretical concern that was outweighed by their desire to remove the limitations of FXS from their son's life, enhance their ability to connect with their son, and enrich his life experience.

> *I would seriously go for a cure anyway because our selfish perception is, "I want what I think is best." I want what I think is best for my child. It's like "what if my child really is happy?" What if he says, "Mom, why'd you take the blindfold off? I was so happy, and now, you know -- I understand, but it's not as great as you thought it was going to for me." You have that philosophical side to it, but then, of course, you have the side where you want to be able to have deep conversations and make sure that they are conscientious, and that they are aware of how the world works so that they can protect themselves, that they can go out and be the most that they want to be and support families if they want to start families, and have deep relationships and whatnot. (Mother 025, Group 2)*

A minority of parents did not find anything "beneficial" or good about their affected child's FXS (Group 1 n=3 Group 2 n=0).

> *I don't think there's anything beneficial about Fragile X. (Father 004, Group 1)*
> *I can't think of any beneficial aspects of Fragile X. I would think that if he didn't have to deal with this pest, that he would be a much happier person, and so would I for him. So, I do not see any benefit to his illness. (Mother 030, Group 1)*

Trial Specific Decisional Factors

In addition to discerning the characteristics and needs of their child in conjunction with their beliefs about FXS, medications, and research, parents also assessed trial factors. The interviews revealed parental deliberation of the experimental drug's

mechanism, expectations and hopes for the trial, barriers and inconveniences of the trial, trial phase, perceived trial purpose and risks, and their degree of trust in the researchers and clinicians involved in the trial.

Purpose of Trial

The purpose of the clinical trial, as perceived by the parents, was found to be another important decisional factor as they considered trial participation. Parents described the purpose of trials to be to develop a drug that would reduce specific FXS symptoms. The most commonly described purposes of trials were to treat all FXS symptoms and develop a cure (Group 1 n=4, Group 2 n=7), treat anxiety (Group 1 n=7, Group 2 n=5), improve attention and focus (Group 1 n=3, Group 2 n=3), modify behavior (Group 1 n=7, Group 2 n=7), enhance cognition and learning (Group 1 n=5, Group 2 n=2), enhance language and communication (Group 1 n=3, Group 2 n=4), and better social skills (Group 1 n=2, Group 2 n=3).

Parents frequently used the trial's purpose in evaluating the degree to which they felt it matched their child's particular symptomatology (Group 1 n=5, Group 2 n=10). Parents were more interested in trials that they believed were targeting symptoms that their child particularly struggled with. Parents who declined trials frequently cited a poor match between the trial's 'purpose' and their child's symptomatology as a significant factor in their decision to decline.

> *I thought it would probably increase his communication ability for sure. But, the enabling of more fluency and maybe some easier communications, we were doing just fine and we were making progress. it wasn't a trial with an outcome ultimately that hit the target of the kind of result that we're looking for. (Mother 002, Group 2)*

> *The purpose of the trial was to see if the medication will work for the targeted symptoms that my adult child had. The social anxiety and anxiety around loud noises, new situations. (Mother 017, Group 1)*

Experimental Drug Mechanism

Parents were aware of the genetic cause of FXS and the efforts to develop a therapeutic targeted at the disease mechanism, likely due to the presence and outreach of disease community-based research funding (FRAXA). Several parents commented on the drug mechanism as an important aspect of trials they had considered, and felt more interested in trials that were evaluating drugs involved in the mGLUR and GABA systems (Group 1 n=5, Group 2 n=4). They felt that these targeted experimental medications were more likely to have a dramatic effect on FXS symptomatology than other medications designed to interfere at the symptom-level rather than the syndrome-level.

> *I was led to participate by the positive outcomes that others had already experienced, the fact that there were such amazing results in some of the laboratory studies, the non-human clinical trials that had come before, and the fact that this drug targeted a known deficiency in his body, and so that we felt like it was -- it made sense to us. (Mother 012, Group 1)*

> *It was a very promising medication that was really -- it was the first of its kind, I guess, at the time -- that was actually targeting the disease process, not just the symptoms. And seeing that my son is on quite a bit of medication, we were excited that this was something that could really get to the mechanism, the functioning in the brain. (Mother 021, Group 1)*

Trial Expectations

When asked to recollect and delineate their hopes (what they wanted to happen) and expectations (what they thought may happen) from the time of decision making, many parents specified a FXS symptom that they expected would improve for their son upon trial participation. Parents in both groups expected to see improvement in their

child's speech and language skills (Group 1 n=2, Group 2 n=2), focus and attention (Group 1 n=1, Group 2 n=1), learning and cognition (Group 1 n=0, Group 2 n=1), behavior (Group 1 n=0 Group 2 n=2), and anxiety (Group 1 n=2, Group 2 n=0). The symptoms that they expected to see benefit infrequently overlapped with their perceived target outcomes of the trial they were considering.

> *I expected that this would decrease my son's anxiety. I expected that going to new places and maybe doing new things would not be as anxiety-provoking. I expected that we might see an increase in his academic performance. (Mother 012, Group 1)*
> *I expected that there would be an improvement in the ability to communicate on the expressive side and that that would create more social and educational opportunities for him. (Mother 002, Group 2)*
> *We expected improvements in language and socialization. We did not expect a miracle from this. But we expected some type of marginal but measurable improvement. (Father 004, Group 1)*

Other parents often described lacking any specific expectations of individual benefit for their child (Group 1 n=11, Group 2 n=2). Many parents described purposefully not forming expectations around individual benefit due to their awareness of the possibility that their son could receive a placebo rather than the experimental drug, as many of the trials parents had considered were double-blind.

> *It was hard to form expectations because we didn't know if he would actually be on the medication or not. (Mother 006, Group 1)*
> *We went in with very -- no expectations, because we don't know if you're getting a placebo, what you're getting. (Mother 019, Group 1)*
> *I went in to it with no expectations and I realize that's the double-blind placebo and my chances are we would get the placebo, so I had no expectations. (Mother 027, Group 1)*

A small subset of these parents shared their lack of expectations of individual improvement to be based upon an understanding that experimental drugs inherently lack sufficient evidence to suggest effectiveness.

Well, I knew it was a trial, so I knew either it would or would not have any effect on his thinking or his abilities. (Mother 017, Group 1)

Some parents who lacked expectations for direct immediate trial benefit to the child did expect the trial to be successful in resulting in an approved effective medication for FXS.

Yeah, I really didn't have any, because it had been explained to me that we could be on a placebo, so I really wasn't looking for anything, and then -- but I did expect that the drug was going to be approved. I was really pretty – I mean, I think all of us had really thought this drug had been vetted and was safe and that it was going to be approved, so that was an expectation that I had, that when the trial would be over that we would be taking this medication because we could get it prescribed. (Mother 032, Group 1)

Yet another common expectation of drug development clinical trials described by parents was a direct non-specific positive effect on their child's FXS symptomatology (Group 1 n=3 Group 2 n=5). These parents were hesitant to define exactly what they expected to change, or how much they thought something would change, but were clear that they thought some aspect of their child's symptoms would noticeably improve.

I expect for something positive that's going to change physically or emotionally. I mean, that's what I would expect from a trial. I want to see something in everyday life change. (Mother 014, Group 2)

I was pretty sure we were going to see something. I wasn't too concerned. I was more curious to see what we were going to see. (Mother 032, Group 1)

A small subset of parents, mostly comprised of decliners, expected negative outcomes from the trial; that the experimental drug would be ineffective or have side-effects (Group 1 n=1, Group 2 n=3).

I didn't think it would work. I thought it would actually cause side effects whether it be seizures or irritability which would actually be worse for my son. (Mother 003, Group 2).

Trial Hopes

Overall, parents spoke more about their hopes for the trials than their expectations, having an easier time describing them. While parents' hopes often overlapped their expectations, they were more specific or grandiose. Similar to their expectations, parents most frequently hoped for improvement in specific FXS symptoms that their child struggled with, however they frequently hoped for a more dramatic change than they expected. Parents in both groups hoped that trial participation would result in significant positive changes in their child's learning and cognition (Group 1 n=9, Group 2 n=3), anxiety (Group 1 n=8, Group 2 n=4), attention and focus (Group 1 n=4, Group 2 n=1), behavior (Group 1 n=4, Group 2 n=4), social skills (Group 1 n=4, Group 2 n=2), and speech and language (Group 1 n=4 Group 2 n=5).

> *Well, I hoped it might improve language. One of the things that I know for certain about those with intellectual disabilities is that they can learn, and they can learn when they're adults, and learning might be much slower but they can learn. So of course, we were hopeful. Maybe, whether or not it would suddenly enable our son to speak, it nevertheless might have encouraged him to communicate more. (Father 004, Group 1)*
>
> *I just expected his ability to communicate to improve in some way. Well, in the perfect world, he'd wake up talking to me. That's what I hoped for. Like, it was all up there and he just couldn't get it all out. (Mother 005, Group 2)*

A group of parents in both groups hoped that the experimental medication would prove to be a cure for FXS (Group 1 n=4 Group 2 n=2).

> *And my hope was that we'd participate in the trial, he'd be getting the drug, and it would do far more than anybody ever expected it would do, and it would basically cure him, and he would come up to me, we'd have a normal conversation like I have with my other children, and then he would have to be pulled out his special needs school because it wasn't appropriate any more unless he needed to catch up. Yeah, and I'd hire tutors to catch up to his normal grade level and that instead of having to have him watched, he could start helping me watch the younger children and that he would become a fully functioning, normal 16-year-old. And if he wanted to go outside, he'd get a smoothie or a bagel for himself, he could just go do that. (Mother 32, Group 1)*

The hope is, you know, the expectation for a drug as I said, like say the goal of it was to replace the FMRP Protein and then essentially take away the effects of Fragile X. (Mother 24, Group 2)
So the hope is that we would see what my son might look like if really Fragile X could be eradicated or reduced. Or taking whatever function he had and really amp it up to see what he is fully capable of with this adjunct therapy. (Mother 021, Group 1)

Barriers to Participation

Parents in both groups discussed several barriers to participating in trials. Many were logistical inconveniences, such as excessive travel to the trial site (Group 1 n=8, Group 2 n=7), high number of required trial appointments (Group 1 n=5, Group 2 n=5), difficulty with scheduling trial appointments (Group 1 n=2, Group 2 n=1), and challenges with taking time off of work to monitor their child throughout the trial and facilitate participation (Group 1 n=1, Group 2 n=3).

It would be a lot better if these trials could be managed locally. If the chosen handful of trial centers could monitor the programs, but have it administered by your local physicians. I think that would be a big deal. Listen, we didn't have to stay in hotels, but, you have a choice. You're trying to drive seven or eight hours all in one day, or is it an overnight trip. If you have other children, you have to make arrangements for them. It became a very trying experience, the actual trial. (Father 004, Group 1)
It typically required travel, and numerous overnight stays for evaluation that just never really fit into our lifestyle. (Father 007, Group 2)
Certainly we did consider having to disrupt not only his school schedule a little bit but our family schedule because we were running to Rush quite a bit. As I mentioned that's a day for us. Three hours down, appointment, three hours back, that sucks up a good day (Mother 028, Group 1)

Another frequently mentioned barrier to trial participation was the necessity of blood draws (Group 1 n=9, Group 2 n=4). Many parents felt that their child struggled significantly with having blood drawn, and some felt it was traumatic for their child. Blood draws were also described as being difficult for the phlebotomists and the parents, as it was often necessary to physically restrain the child in order to draw blood. Some

parents declined any trial that involved blood draws, and others described it as the primary aspect of trial participation that they did not like.

> *The main thing is that if it involves blood work, I didn't even -- I mean, that was my first question. Does it involve blood work? If it did, I didn't even consider it. (Mother 001, Group 2)*
> *Another one of my big issues with clinical trials is my son will not tolerate blood draws. And so I will not put him through that PTSD of having a blood draw. It's very traumatic for him. (Mother 024, Group 2)*
> *The only part of participating that I was unsure about was the required blood draws, because of the trauma that that causes for my son. (Mother 027, Group 1).*

Some parents were concerned about trial requirements to discontinue use of regular medications throughout the trial period (Group 1 n=3, Group 2 n=4). A subset of these parents was unable to participate in a trial due to significant concerns about taking their child off of medications, such as seizure medications.

> *When we found out what was involved, making the decision about the trial was excruciating. That was pretty awful. They are on a lot of medication. With our son, it was going to take three months to wean him off his current medication before we could even get to participate. And then he was going to have to be off of everything for a certain amount of time. And then we could get the medication, whether it was real medication or not. We would have to take them out of school, because they couldn't function. We wouldn't be able to go anywhere because we couldn't guarantee their safety anywhere. That was really scary. This is back to the beginning, when my son would throw himself down in the parking lot and scream and cry. And I'd worry about him hitting his head on the cement, not to mention that it's a hundred degrees -- you can fry an egg on the sidewalk. So, are they going to be hit by cars? You just can't guarantee their physical safety. So that was a huge concern. Was I going to have to quit my job and stay home with them? What we were going to live on if I had to quit working? So there would be all this time to wean them off the medication, and then there would be all this time with no medication, and then we wouldn't know -- it would be like six weeks we would possibly be on the placebo and we're getting nothing. (Mother 018, Group 2)*

Risks of Trial

The most commonly described anticipated risks of drug development clinical trials were physical side effects (Group 1 n=14, Group 2 n=13). Some parents described risk of unknowable side effects, while others were aware of specific side effects that they perceived to be associated with the experimental drug in question. Concerns about side effects were a significant deterrent from trial participation for parents in both groups.

> *There's always a side-effect with medication and so, those were the risks we were most concerned about. There were not really any specific side effects we were worried about. We were worried just generally. (Mother 006, Group 1)*
>
> *I guess there were always the unknown risks of a medication. I don't think I knew of any specific risks. (018, Group 2)*
>
> *I wasn't really for it because, down the road, you just never know. After you put that in your body, over time, you just never know. Down the road they might say -- I mean I hate to say this because it can happen with anything, I mean anything you do in life you take a chance. But, down the road they could say, "Well, that drug now causes seizures, or causes cancer, or causes kidney failure." So I really didn't want to try it. (Mother 026, Group 2)*

Many of the parents in Group 1 considered risk of side effects to be low despite mentioning them as the main risk of participation (Group 1 n=8), while many of the parents in Group 2 considered side effect risks to be more severe (Group 2 n=9).

> *It had that B vitamin thing, and all that and stuff I had heard about that they were wondering was doing good, but the side effects that they were seeing was real mild, so it was like the risk factor, for me, was so low that I said, "I can do this one." (Mother 013, Group 1)*
>
> *And knowing that it was based on a med that's already on the market and used since the 1920s, I felt that the risks of side effects were very minimal. No worse than some of the medications he's taken on the market now. (Mother 029, Group 1).*
>
> *So, the one thing about minocycline that you don't really hear much about, and I've actually spoken with my son's dermatologist about is that extended use of minocycline can cause graying of the mouth and even the face. It's been – it's permanent. I actually spoke with his physician about that one time. Even as an adult, not just graying of the teeth. We're talking graying of the inside of your mouth and of your actual face -- the skin on your face. So, I know that that's a risk. (Mother 001, Group 2)*

A subset of parents were concerned about the inability of their child, due to age and/or symptomatology, to communicate pain or discomfort indicative of a side-effect or adverse reaction to the experimental drug (Group 1 n=1 Group 2 n=4).

> *And then they're not really able to tell you if they're uncomfortable, if they don't have that language capacity already. And so it was hoping that we would notice if there was anything wrong. (Mother 008, Group 2)*

Phase of Trial

Overall, parents were found to have a low level of concrete understanding about the phases of drug development clinical trials. Accordingly, the trial phase was not a primary decisional factor. When asked what they thought about phases of trials, parents believed that the phase was related to the age range of participants (Group 1 n=5, Group 2 n=5), whether the trial was determining safety (Group 1 n=7 Group 2 n=4), whether the trial was determining efficacy (Group 1 n=5, Group 2 n=2), whether or not participants had the target disease (Group 1 n=1, Group 2 n=2), whether or not participants may receive a placebo (Group 1 n=3, Group 2 n=7), and the FDA approval process (Group 1 n=5, Group 2 n=6).

> *So I think in -- yeah, I don't know. So my understanding is that in phase one, maybe it's adults. Yeah. And I know that they check for signs and symptoms and different things like that, and side effects. Then I think -- yeah, I don't know. Phase two, I think, is maybe more people; I don't know. Yeah, I don't know. (Mother 012, Group 1)*
>
> *To me, phase III meant that it was safe. And that there was some idea that, in his dosage range, they would get some sort of result, measurable results. (Father 004, Group 1)*
>
> *Phase one is the initial phase for toxicity. Phase two is an initial trial for efficacy, and then phase three is, to really see whether or not it can be used outside the market, I guess. (Father 010, Group 1)*

You know, that's a good question because I don't know what phase 2 means. I think that means that it's been -- I don't know whether it's been tried in animals, or in typical people. So, that's a good question. I don't know. (Mother 001, Group 2)

I don't know much about how phase works because I've never participated in it. (Mother 026, Group 2)

The phase of the trial was very important, however, to a subset of parents. These interviewees were hopeful that participation in a phase two or three trial would mean that the experimental drug would likely be FDA approved and available long term for their child (Group 1 n=6, Group 2 n=0).

We agreed to do this trial because it was in phase three. Because we were told that, like everyone else, that once the trial was over we would get the medication if it helped our son. That was my biggest deciding factor and why we decided to do the trial. (Mother 019, Group 1)

I think it was second phase and I knew that if it worked out or if we had enough information right after the study that the drug might actually go on, it could actually get approved by the FDA. (Mother 017, Group 1)

Trust in Trial Personnel and Institutions

Fifteen parents described their degree of trust in the personnel and institutions involved in the trial (researchers, clinicians, clinics, and pharmaceutical companies) to be a significant decisional factor as they considered drug development clinical trials for their child with FXS. Parents in both groups who had negative experiences with having their child in a drug development trial in the past felt their trust in these personnel and institutions had suffered as a result.

We are living in times where every institution that we've come to depend on has not just disappointed us, but it's just outraged us. And there is no trust in anything. (Father 004, Group 1)

Then there's the trust issue, you know? Lay it on us. I want the good, the bad, and the ugly because if there's not that presented in the way that's expected then there's no trust. Especially when it's -- you're also learning. You're new enough or newer to this realm and feeling that you're not as experienced and don't know enough to make a properly informed decision. (Mother 002, Group 2)

Some parents in Group 1 explained that their high level of trust in the researchers and clinicians involved in the trial, based on long-term relationships with the trial site or awareness of the head researcher's work, strongly influenced their decision to participate.

> *I really just spoke to the clinical trial doctor, and the woman I knew from the Elwin group was actually, I think, the study manger, so I had already known her as well. Which was nice, so that kind of gives a comfort level. (Mother 033, Group 1)*
> *I think it was just that we trusted the process. We trusted our doctor who was involved in the study. (Mother 021, Group 1)*

Decision Making Process

Parents were asked to reflect on their decision making process around drug development clinical trial participation. As they considered their decision making process, most parents remarked on weighing the risks and benefits of the trials. Family, friends, and health care providers were found played roles in the decision making process for interviewed parents.

Weighing the Risks and Benefits

Parents in both groups assessed their perceptions of the potential risks and benefits of the trials in making the ultimate decision whether to enroll their child. Parents in Group 1 tended to feel that the potential benefits outweighed the potential risks, while parents in Group 2 tended to feel the opposite.

> *You know, it's like anything else. You just -- do you think we should this? As I said, we thought -- we saw little or no risk so based on that and based on a possibility that it might do something good, we went forward with it -- the decision. (Father 004, Group 1)*
> *Anytime anything will benefit our children, we lean toward that automatically. So, the decision, once we looked at the risks and the benefits, and the potential for other children with Fragile X, it was easy to make a decision to participate. We felt like the risks were minimal compared to the benefits. (Mother 006, Group 1)*
> *When you're deciding, you really need to take the time, like, really weigh out all the pros and cons and really figure out "is the risk worth it?" Is it really -- I mean, you know your child. You really*

have to really weigh out "is the possible benefit definitely more than the possible risk that is involved?" and if you can say yes to that, if your child is, very regressed or on the low end or whatever, then "okay, I think it's worth the risk if the benefit is there," if this means my child can speak and my child can go to the bathroom on their own, my child can interact with other people, if that's worth "oh, my gosh, my child now has a problem with their kidneys" or whatever. I really have to weigh it out. (Mother 025, Group 2)

Roles in the Decision

Most parents described making clinical trial decisions primarily alone or with the support of their partner. Parents found informational support in the researchers and clinicians involved in the trial (n=13). Most interviewed parents were notified about trials remotely, through support group e-mails or mailed flyers from clinics. They would deliberate the trial independently, and reach out to the researchers and clinicians involved in the trial for more information as needed.

It's probably a conversation with my husband. Like when I say probably, the fact that I was the one bringing him in, it was more -- it was a joint decision between my husband and I, but it is probably more on me, because I was the one committing to bring him in and everything. (Mother 33, Group 1)

The clinic doctor explained what was involved and sent the information. And we had talked about it and stuff. She expressed excitement about it, but she did not push me into doing it. (Mother 003, Group 2)

I talked to his doctor, and he said he thought it would be okay. I talked to the doctor who ran the study; I called to him first and he explained what it was and what it would target. I think I read a little bit online about this study. Talked about it with my husband, asked my son and he said he would be fine with it, he would do it. And after that, we were in. (Mother 017, Group 1)

Many parents did not feel that any health care providers played a significant role in influencing their decision. In particular, several interviewed parents described their child's primary care physician, pediatrician, or psychiatrist to play no role in the clinical trial decision-making process (n=21). These parents did not feel that this physician had

adequate knowledge about FXS to contribute significantly to the decision, and described instances in which they had to educate this doctor about FXS in the past.

> *I'd probably talk to his psychiatrist about it, and just say, "I'm thinking of doing this. What do you think?" And see what she says. I mean, I'm the one educates her about Fragile X and so, she would probably be fine with whatever I said. But it would be just another view point. It'd be another source of information. I might talk to his primary doctor, but he's just a primary doctor. I mean, we just go to him for earaches, headaches. Kind of like I would say to his psych, I would just use her as a source of information but she wouldn't, at this point, help make the decision. My husband and I would. (Mother 001, Group 2)*
>
> *I don't know that our day-to-day treaters -- pediatricians, internists -- would be qualified. And I don't know that I would take much of what they had to offer, because we know more than they do. (Father 009, Group 2)*
>
> *Nobody helped me make the decision. The doctor, she gave me information (Mother 013, Group 1)*
>
> *It's really pretty much been myself, because, to tell you the truth, so many doctors don't even know much about Fragile X. I probably know more about it then the doctor. (Mother 026, Group 2)*

A subset of parents reported that other parents of children with FXS played an important role in their decision-making process, as they consulted with parents who had experience with some aspect of the trial, such as the experimental medication or the primary researchers (Group 1 n=5, Group 2 n=4).

> *Listening to other people like, my Facebook community is a lot of parents who have children with Fragile X Syndrome. So we always discuss different topics and different things, and that's opened my eyes a lot, like, okay, the trials might be worth it. And that's why I have been looking into them way more than I had and seeing that it's not going to hurt him. Like, it's not going to be this painful thing or anything like that. So if you ask me today, I'm actually willing to give a trial some consideration as long as I know that it's not going to physically hurt him. (Mother 014, Group 2)*
>
> *We talked to everybody and anyone who was on the trial. "What are you seeing? What is it doing? What is it like?" I would say honestly the major thing was hearing from other people that it was working and also knowing we would get the medication. (Mother 019, Group 1)*

Parents were also asked whether their child with FXS played a role in the decision. Nineteen parents representing both groups felt that their child played no role whatsoever in the decision-making process. Their child's lack of influence in the decision-making process was attributed to their child's inability to understand, either due to their young age or degree of affectedness.

> *My son's role is very minimal because he's too little to really understand the concept of a clinical trial. (Father 010, Group 1)*
>
> *He doesn't have the cognitive ability to make any decisions. (Mother 027, Group 1)*

The remaining parents described ways that their child with FXS played a role in the clinical trial decision-making process, however most of these roles were limited. Parents reported that their son with FXS played a role in the decision in relation to one aspect of participating, such as travel, acceptance of taking medications generally, or communicating pain or discomfort that could be indicative of side effects.

> *My son played no role. Except indirectly. Just judging how he felt about clinical trials. I almost considered doing it because he had enjoyed the process. So he'd probably like doing it again. But, yeah he didn't have much of a role because he can't express himself that way. (Mother 003, Group 2)*
>
> *Well, I asked him, does he want to go back and forth or not? At first he said yes. And so, that's when I said yes because he did. For the second trial, at first he said yes but then I started talking to the manager of the study, and she couldn't be very flexible with the times and it was just too hard to try and get everyone's schedule to wrap around her schedule, which was inflexible basically. (Mother 016, Group 2)*

Decisional Conflict and Regret

Overall, parents expressed a range of conflict but low regret about their clinical trial decisions. Sixteen parents found making the decision relatively easy compared to other decisions in their lives (Group 1 n=10, Group 2 n=6). Parents who found the decision to be easy were primarily parents in Group 1 who were more focused on the

potential positives of participating and cited very few negatives (Group 1 n=10) or were parents in Group 2 who expressed strong beliefs against medicating their child (Group 1 n=0, Group 2 n=3), or cited disinterest in the experimental drug's mechanism (Group 2 n=3).

> *The decision was pretty simple. Based on what it was doing, they weren't doing anything like a medical and if there were some type of adverse reaction, we would just immediately have to stop. And it's kind of -- it's a lot of pressure as [a single person], because I have to make all those decisions, and I don't have somebody to kind of throw it back and forth with. But other than that, just the fact that it could not only help him, but that this study could also help other people that have younger children. Maybe it helps, and then it can help them. (Mother 015, Group 1)*
> *It has always been a really easy decision for us because we've never really had the desire – seen the need or had any desire to start him on any medications. So that made the decision pretty easy to not participate (Father 007, Group 2)*

Another group of interviewees found the decision to be hard (Group 1 n=4, Group 2 n=6). These individuals were often focused on risks and barriers that prevented them from participating despite a desire to do so. Six parents reported finding the decision to be moderately difficult - not particularly hard or easy (Group 1 n=3, Group 2 n=2).

> *It was moderately difficult to make the decision. Easy because I was so eager to find help for him and I wanted to find a drug that could possibly help. Hard were the side effects and possible mind-altering state they kept on talking about. (Mother 017, Group 1)*
> *It was difficult for me to not participate because they're making progress in this area, like huge progress. I think about when this was discovered and it hasn't been that long and they're on drugs that they want to try on individuals with it. I'm very excited to hear that things are happening that fast. I wish that we could participate. (Mother 005, Group 2)*

All parents in Groups 1 and 2 reported feeling as though they made the right choice given what they knew at the time. Even when the trial experience was challenging, or the experimental drug was ultimately determined to be ineffective, parents in Group 1 perceived benefits in their participation. In these circumstances, many parents explained

that they made the right choice because their participation helped move the science forward, and they often perceived benefits of participation outside of the effects of the drug, such as learning more about their child or gaining access to resources and information.

> *Oh, no doubt. Of course I feel I made the right decision. Because I loved the changes I saw in him. So, he didn't walk in totally cured. I loved the subtle changes, and that gave me a glimpse of what the future could look like. I had to moderate what I was hoping for, but when I got through that, it definitely gave me a glimpse of what the future could look like. And then the other thing is that I just felt good about having participated, because I know how important it is. Without clinical trials, you don't get drugs on the market. (Mother 032, Group 1)*
>
> *Well, because even though the study failed, I feel that there was a lot of good information gleaned from the million parent surveys that we filled out and the blood draws, not just from my son, but from all of the participants. And anything that we can do that adds to their body of knowledge about Fragile X and can possibly lead to other, more successful drug trials, then that's not wasted effort. (Mother 012, Group 1)*
>
> *Yes, I feel I made the right decision. Because in the end it didn't work out, and it was taken away from everyone. (Mother 018, Group 2)*
>
> *I think I made the right decision and that's been reinforced by other people that I've talked to who have been on those trials and the money was pulled and they saw great things happening from being on those medications and then the drug companies said, "due to funding we're not going to be able to continue with this medication or pursuing it." And the family was devastated. Because they felt like they had finally gotten their son and gotten to know who he was and then they were taken off and they were devastated. And so for me, I was like that's exactly what I expected and that's exactly -- that was pretty painful for them. Extremely painful. Like I don't think they'll evert trust anybody with Fragile X research again. Like the foundation, or the drugs, or any of it. They were devastated. (Mother 024, Group 2)*

DISCUSSION

Overall, parents of children with FXS report deliberating a number of factors throughout their clinical trial decision-making process. Our study revealed that parents assess these factors by weighing the potential risks and benefits of participation, and seek informational support from clinicians and researchers involved in the trial. This decision making process leads these parents to their decision, to either enroll their child in a trial (constituting parents in Group 1), or decline to do so (constituting parents in Group 2). Decisional conflict ranged among parents regardless of group, with some finding the decision-making process to be difficult, and others finding it to be easy. Despite the degree of difficulty involved in making a decision, upon reflection, all parents in our study ultimately reported feeling that they made the right choice for their family and did not feel regret.

The identification of specific factors involved in parental decision-making for FXS clinical trials can be used to generate hypotheses for future quantitative research aimed at measuring the effect of these factors on the decision making process and outcomes such as decisional conflict. These downstream studies can then provide the data for designing evidence-based interventions to facilitate the decision making process.

Decisional Factors and Process

Prior research has identified contextual and trial-specific decisional factors for pediatric clinical trial participation for physical health conditions (asthma, sickle cell disease, and vesicoureteral reflux) (Barakat et al., 2013; Hoberman et al., 2013). Our study revealed several prominent contextual and trial-specific factors parents of children

with FXS consider as they deliberate trial participation. In general, parents in our study had strong attitudes about medicating their child for FXS, and these attitudes appeared to influence decision making about drug development clinical trial participation. Some parents who had declined trial participation were found to avoid medication for FXS symptoms altogether, while on the other extreme, some parents who had elected trial participation were found to embrace it as a critical component of caring for their child. While drug development for rare diseases frequently encounters barriers in recruitment due to relatively small study populations, the variance observed in our study around the FXS community's interest in medication may constitute another barrier in acquiring adequate numbers of clinical trial participants for this disease context.

Furthermore, as parents with strong positive attitudes towards medication are more interested in participating in drug development trials, their child is likely to already be on medications. Our study revealed difficulty in ceasing use of medications throughout the duration of the trial, with some parents who had declined participation citing this challenge as a primary motivation to decline. Future drug trials could benefit from minimizing time off medications and communicating clearly about this need to parents.

As FXS is primarily psychological and cognitive rather than physically disabling or life-threatening, parents appear to be more risk averse to medication side effects and drug development clinical trial risks compared to what has been observed in parents of children with life-threatening progressive conditions (Peay et al., 2014). As parents of children with FXS struggle with managing their child's condition in many ways, some decliners in our study appeared to use a downward social comparison (comparing their

situation to that of parenting a child with a life-threatening chronic condition) in their coping processes, and expressed particular gratitude for the physical health of their child. Prior research has characterized the use of downward social comparison in coping with chronic health conditions (Arigo et al., 2014). Parents of children with FXS may be particularly resistant to any risk of harming their child's physical health as social comparison may be one way they cope effectively. Parents of children with life-threatening conditions, conversely, are faced with relatively little to lose in this domain, and medication side effects may be perceived as less harmful for their child when compared to the untreated disease course.

Our interviews also revealed the potential benefit of the drug to be a primary decisional factor for parents of children with FXS considering clinical trials. This is consistent with prior research exploring decisional factors involved in parental decision making for pediatric clinical trial participation for physical ailments (Barakat et al., 2013; Hoberman et al., 2013; Markward et al., 2013). In our study, we found that parents who had both declined participation and elected participation evaluated the potential benefit of the drug through their perception of the drug's mechanism of action and the degree of match between the purpose of the trial, which they described as developing a drug that would reduce specific FXS symptoms, and their child's particular symptomatology. To determine this match, parents generally considered what they were struggling most with in caring for their child. For example, parents who were raising a child who is nonverbal frequently mentioned higher interest in trials with communication as the target symptom, and parents who were raising a child who was exhibiting violent behaviors sought trials which targeted behavioral outcomes. These parental evaluations of the potential for

individual benefit from the drug, based on drug mechanism and degree of match between target symptom(s) and child symptomatology, formed hopes and expectations for the trial for parents in both groups, as well as the primary motivations behind electing participation amongst parents who had elected participation for their child. Some decliners cited a poor match between their perception of the trial's purpose and their child's symptomatology as a primary motivation for their declining participation.

Consistent with prior research in other disease contexts (Peay et al., 2014; Jansen et al., 2011), there was evidence of therapeutic misinterpretation in our study. The expectations of parents who had elected participation were often high and described in terms of potential for individual benefit. The purpose of trials was also generally described in terms of individual benefit rather than an effort to contribute to scientific knowledge. Nevertheless, parental understanding of trial goals was expressed in the interviews, as we also observed altruistic motivations and perceived participation benefit in contributing to scientific knowledge amongst parents who had elected participation.

In line with prior work (Peay et al., 2014; Weinfurt, 2003; Jansen et al., 2011), our observation of therapeutic optimism and misinterpretation seems to be a result of parents' emotional engagement with trials, and dissonance between cognitive and emotional understandings. Past research has suggested phase 1 clinical trial expectations to be related more strongly to personality variables (such as high trait optimism) than knowledge about clinical trials (Weinfurt, 2003). Furthermore, psychology research has uncovered the relevance of unrealistic optimism in clinical trial decision-making. Unrealistic optimism, when one thinks that one is more likely to experience positive outcomes than others similarly situated, is a type of situational optimism with both

cognitive and affective determinants. In a study of patients enrolled in early-phase oncology trials there was no significant relationship between unrealistic optimism and misunderstanding about the purpose of clinical trials, and more participants exhibited unrealistic optimism than therapeutic misconception. Thus, optimistic biases are understood to be an independent explanation for patients' expectation of therapeutic benefit from clinical trial participation that is not reliable on lack of knowledge or misconception (Jansen et al., 2011), and is a likely explanation for the therapeutic misinterpretation observed in our study.

The logistics of participation constitute an additional major decisional factor for parents considering clinical trial participation. This has been observed in previous work evaluating the decisional factors involved in pediatric clinical trials for physical conditions (Barakat et al., 2013). Our study revealed several barriers to participation that could prevent parents from electing to participate despite their hopes for a highly beneficial drug. Most prominently, parents who had declined trial participation were deterred from enrollment when the trials involved a greater burden on their time, through excessive travel to the trial site or high number of required appointments. In addition, parents of children with FXS are highly concerned about the necessity for blood-draws in trials, as it is common for affected children to be resistant to having blood drawn. Perceived risks of side effects constituted another barrier to participation, with parents of severely affected or young children expressing particular concern that their child would be unable to communicate pain or discomfort indicative of side effects. The presence of these barriers constituted the most common motivations for declining trial participation amongst parents who had declined.

These findings have many practical implications for the design of future drug development clinical trials for this rare disease. Our study revealed a need for FXS clinical trials to feature an increased number of clinical sites with better distribution across the country and minimization of appointments and blood-draws required for families where possible. Additionally, the concerns of parents with young or severely affected children around their child's ability to communicate pain or discomfort indicative of side effects should be addressed in future trials. For example, parents may be educated about nonverbal signs of pain or discomfort, assured that clinicians involved with trials will know how to assess pain and discomfort for all participants, provided guidance in teaching their children to use communication aides, or reassured that the study's evaluations would involve monitoring for side effects.

Overall, our study suggested parents' decision making processes to involve a weighing of these decisional factors, framed as potential risks and barriers and potential benefits of participating. Parents in both groups primarily made these decisions either alone or with the support of their partner. Only clinicians directly involved in the trial were mentioned as providing significant informational support. Parents did not feel that their child's primary doctors were qualified to assist with clinical trial decisions, and the only friends that were involved in the decision were other parents of children with FXS.

Consistent with previous work that evaluated parental ratings of affected individuals' ability to consent for clinical trials (Bailey et al., 2014), a significant portion of parents felt that their child was not at all capable of participating in the trial decision making process, and the vast majority of remaining parents found their child to have a significantly limited role in the decision.

Decisional Conflict and Regret

Our study was also able to describe levels of parental decisional conflict and regret over the drug development clinical trial decision making experience. Decisional conflict was found to range in both groups from low to high, with some finding the decision to be easy, some finding it to be hard, and others finding it to be moderately difficult. Those who found the decision to be easy were more often parents who had elected participation and were focused on the potential positives of participation or were parents who had declined trial participation and hold strong beliefs against medicating their child. Those who found it to be a hard decision were often focused on the presence of barriers or risks that conflicted with their desire to participate. This contrasts with prior qualitative research in Duchenne muscular dystrophy, which observed low decisional conflict overall, with most parents finding trial participation to be a 'non-decision' (Peay et al., 2014). This difference is likely to be due, in part, to the fact that DMD is a progressive, fatal disorder. In addition to these differing emphases of decisional factors, it is possible that parental personality traits influence decisional conflict levels.

Decisional regret was found to be remarkably low in our study. This is consistent with prior research that found low decisional regret amongst parents who had elected to enroll their child in Duchenne muscular dystrophy trials (Peay et al., 2014), as well as a systematic review of the extent and predictors of regret in health decisions (Perez et al., 2016), which concluded decisional regret to be low for most health decisions. Because the ability to experience decisional regret relies upon individuals understanding of the counterfactual of what outcomes would have resulted from a different decision, it is

possible that low decisional regret is the result of parents' inability or psychological resistance towards perceiving this counterfactual.

Implications for Future Research

This qualitative study has generated hypotheses that can be explored in future research. First, a quantitative survey study involving a larger sample of parents of children with FXS (representing both participants and decliners) should query the primary decisional factors that were revealed in this study; parental attitudes towards medicating their affected child, perceptions of the potential benefit of the drug for their child (including the degree of match between the trial's target symptom(s) and the particular symptomatology of the affected child, and parental perceptions of the drug's mechanism of action), and the presence of identified barriers to participation (i.e. logistics and blood-draws). Quantifying these factors in conjunction with decisional outcomes such as conflict and regret, and additional parental characteristics, such as personality traits, will allow further elucidation of the ways they influence the decision making process, the ultimate decision, and these outcomes. Such a study may also examine the impacts of affected children, health care providers, and other parents of FXS in influencing parental trial decisions.

Further research should assess the effectiveness of decisional interventions, such as shared decision-making counseling interventions with health care providers or decision-aides to be completed by the parents independently. These aides are used to clarify the decision-maker's weighing of potential benefits and barriers or risks involved in the decision, and could be informed by the specific decisional factors identified in our study to be tailored to FXS drug development clinical trial decision making. Helping to

clarify parental feelings about these factors may assist them throughout their process of identifying the best choice for them.

Finally, parental perceptions of the likelihood for development of a remarkable disease modifying or curative therapy should be explored further. Our interviews revealed a history of high community hopes and subsequent devastation with the abrupt termination of several trials due to failure to meet outcome measures or loss of funding despite parental perceptions of benefit. Further understanding of this experience and its effect on the broader community will enhance understanding of parental decision making for FXS drug development clinical trial participation.

STUDY LIMITATIONS

This study has several limitations. First, participants were recruited from the support groups, the National Fragile X Foundation and the FRAXA Research Foundation. Therefore, this study is limited by selection bias as participants recruited from these organizations may have access to more resources than the general population of parents of children with FXS, and thus have an enhanced ability to consider trials regardless of participation barriers (although our data do not seem to indicate this). Participants who are active with these support groups may also be relatively well adapted to life as a parent of a child with FXS, and have higher family functioning, both of which may influence clinical trial decision-making. Due to FRAXA's investment in developing a cure for FXS, participants recruited through this group may hold extreme views about the potential for the development of a disease-modifying therapy and the meaning of drug development clinical trial participation. Second, our study is limited by self-selection bias, as participants who expressed interest in our study may over-represent the parents who are most comfortable with their trial decisions and accordingly more willing to discuss their decision-making experience in an interview, or most passionate about the choice they made. Our sample may have also underrepresented parents who are not interested in or distrustful of researchers.

Third, participants may have been motivated to answer interview questions in ways that are most socially accepted or desirable rather than expressing their true thoughts and emotions. Fourth, recall bias is a significant limitation, as many participants were reflecting on decisions that occurred years ago. Participants were only able to answer the interview questions based on what they remembered, which may have been

limited by what they preferred to recall. Furthermore, many participants in Group 2 did not recall the specifics of the trials they had experience with declining. This has limited our ability to draw some conclusions from the decliners we interviewed, and causes further concern of recall bias.

CLINICAL IMPLICATIONS

The experiences reported by parents in this study raise important clinical implications for healthcare providers working with parents of children with FXS. Drug development research has permeated FXS support group environments, and parents are facing continued clinical trial information and invitation. Clinicians and support group personnel may discuss the primary decisional factors uncovered in our study with parents of children with FXS regardless of whether a particular trial is being deliberated. Parental clarity around these decisional factors may enhance parental decision making processes and reduce undesirable decisional outcomes, such as regret and conflict. Open communication and information exchange with healthcare providers is likely to assist parents as they navigate these environments.

Furthermore, connection between parents of children with FXS has been revealed to be important in parents' decision making process, as other parents of children with FXS were found to play significant roles in the decision for many interviewees. Clinics can facilitate and encourage these connections but also make sure they are informed, using high-quality educational materials directed to an informed lay audience. Our study also revealed a low level of understanding of clinical trial phases and true purposes. This warrants effective educational intervention from health care providers as needed.

There are also implications for healthcare professionals working with parents of children with autism or intellectual disability, as these disease contexts share many commonalities with FXS. Specifically, our findings around parental attitudes towards medication, relative risk aversion compared to parents of children with physical or life-threatening conditions, the limited role of the affected child in the trial decision making

process may apply more generally to ID. Some of our findings may be more specific to FXS. For example, it is likely that parental perceptions of drug mechanism of action is likely to play a decisional factor for parents of children with FXS but not parents of children with ID generally, as all parents of children with ID are not unified by a single disease mechanism.

In the event of drug development clinical trial invitation for parents of children with these more common conditions, healthcare professionals may elicit discussions with these parents around the decisional factors uncovered in our study, provide patient education around trial phases, goals, and processes, and facilitate access to peer support.

CONCLUSIONS

This study described parental decision making for FXS clinical trials. Our findings revealed primary decisional factors that these parents weigh in their decision making process, and explored the decisional outcomes of conflict and regret. Parents primarily consider their background attitudes towards medication, the potential for individual benefit from trial participation (through evaluating the drug's mechanism of action and the degree of match between the trial's target symptom(s) and their child's specific symptomatology), and the presence of specific logistical barriers and side effect risks in their drug development clinical trial decision making process. The potential for individual benefit from trial participation largely shaped parents' expectations and hopes for the trial, leading to high therapeutic optimism amongst parents who had elected participation. Our findings shed light upon parental proxy decision making for clinical trial participation in the disease context of intellectual disability, and generated hypotheses for future quantitative studies aimed at ultimately developing interventions to facilitate this decision.

APPENDIX A: RECRUITMENT LETTER

Dear community members,

We are seeking parents of people with FXS to participate in a research study on parental experiences and decision-making about FXS drug-development clinical trials. The goal of this research study is to explore the personal story of parents who have experience with FXS drug-development clinical trials.

Little is known about how parents make decisions about these trials, or how the trials impact the experience of parenting an individual with FXS. We hope this study will provide insight into the needs of parents who are making these decisions or are currently participating in a trial so that better care can be provided in the future.

The study involves phone interviews with a parent of an individual with FXS. Each interview will last about 30-45 minutes long and involve questions about the experience of making a decision about clinical trial participation or the experience of clinical trial participation itself. We will also collect general demographic information.

If you are a parent of someone with FXS (of any age), you can take part in the study if:
-You are 18 years of age or older and speak English.
-You have a child who was enrolled in a drug-development clinical trial for FXS in the past OR…
-You have declined an offer of drug-development clinical trial participation for your child with FXS

Out of respect for volunteering time for the interview, participating parents will be sent a $15 Target gift-card.

If you are interested in participating in the study or would like more information, please contact the research fellow, Celeste Schepp D'Amanda, by e-mail. Thank you for your time and consideration to take part in this study. We look forward to hearing from you.

Sincerely,
Celeste Schepp D'Amanda, BA
Research Fellow
JHU/NHGRI Genetic Counseling Training Program
celeste.d'amanda@nih.gov

Barbara Biesecker, PhD
Principal Investigator
Social/Behavioral Research Branch
NHGRI

APPENDIX B: RECRUITMENT WEBSITE

National Human Genome Research Institute

Fragile X Syndrome Clinical Trials: Expectations, Hope and Decision Making of Parents

We invite you to participate in a research study on how parents of people with fragile X syndrome (FXS) experience and make decisions about FXS drug development clinical trials. The goal of this research study is to explore the personal story of parents who have experience with FXS drug development clinical trials.

Little is known about how parents make decisions about these trials or how the trials impact the experience of parenting an individual with FXS. We hope this study will provide insight into the needs of parents who are making these decisions or are currently participating in a trial so that better care can be provided in the future.

The study involves phone interviews with a parent of a person with FXS. Each interview will last about 30-45 minutes and involve questions about the experience of making a decision about clinical trial participation or the experience of clinical trial participation itself. We will also collect general demographic information.

If you are a parent of a person with FXS (of any age), you can take part in the study if:

- You are 18 years of age or older and speak English.
- You have a child who was enrolled in a drug development clinical trial for FXS in the past **OR ...**
- You have declined an offer of clinical trial participation for your child with FXS **OR ...**
- You are currently considering drug-development clinical trials for your child with FXS.

Out of respect for volunteering time for the interview, participating parents will be sent a $15 Target gift card.

If you are interested in participating in the study, or would like more information, please contact the research fellow, Celeste Schepp D'Amanda, by email.

Thank you for your time and consideration to take part in this study. We look forward to hearing from you.

Sincerely,

Celeste Schepp D'Amanda
Research Fellow
JHU/NHGRI Genetic Counseling Training Program
Email: celeste.d'amanda@nih.gov

Barbara Biesecker, Ph.D.
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Research Coordinator
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NHGRI

Last Updated: September 1, 2016

APPENDIX C: RECRUITMENT FLYER

APPENDIX D: INFORMED CONSENT SCRIPT

Parental Experiences of FXS Drug Development Clinical Trials
INFORMED CONSENT

First, we would like you to know that: Taking part in this research study is entirely voluntary. You may choose not to take part, or you may stop being in the study at any time.

The purpose of this study is to help researchers learn more about the experience of parental decision-making about drug-development clinical trial participation for their child with FXS. Our goal is to identify the needs of parents in this situation and improve care for future parents.

You have been asked to join this study because you are a parent of an individual with FXS and you have experience with drug-development clinical trials for FXS.

You can take part in the study because

-You are 18 years of age or older and speak English
-You have a child previously enrolled in a drug-development clinical trial for FXS

or

-You have declined clinical trial participation for your child with FXS.

The study involves a phone interview that will last about 45 minutes. The interview will be tape-recorded. All identifying information will be removed from written transcripts of the interviews. We will also collect general demographic information.
There are no physical risks of taking part in this study. However, it is possible that some questions may make you feel upset or anxious. If you should feel upset at any point during the research interview, you may stop participating. If you feel upset after completing the interview, you may contact the researchers.

There are no direct benefits to you from taking a part in the study. However, the information you provide to us may help improve our understanding of the experience of a parent of an individual with FXS. We may be able to use this to inform future studies that aim to improve the process of clinical trial decision-making.

You are a volunteer in this study and may stop it at any time. During the interview you may also choose to skip any question that you do not wish to answer. If you decide to stop being in the study during your interview, all of our collected information about you may be permanently destroyed. After the interview is complete, we will not be able to destroy the information from your interview.
Once you are enrolled in the study you will be assigned a unique participant ID number. This ID number and not your name will be used on forms with the information we collect; all paper forms will be accessible only to the researchers. Audiotapes will be destroyed once transcribed and the transcriptions proofread; any identifying information

such as names and specific locations will be removed or changed. We will not share any identifiable responses with outside parties.

Do you have any problems or questions about this study or about your rights as a participant?

If you agree to the terms of the study and are willing to participate, you may proceed to verbally consent. Your consent means that you have been informed of the study's purpose, its procedures, and the possible risks and benefits. Your consent means that you have been given a chance to ask questions before you consent. Your consent means that you have voluntarily agreed to be in this study.

APPENDIX E: SOCIODEMOGRAPHICS FORM

Socio-demographics

First I would like to obtain some information about you and your family.
Are you a father or a mother of a son with Fragile X syndrome?

Are you your son's biological or adoptive parent?

For biological mothers- what do you know about your FMR1 carrier status?

How much formal schooling have you had?

Did you finish high school? College? Professional School?

How do you define your race?

Are you married?

How many children do you have?

Briefly tell me about all the trials you have decided about. [Review list of considered clinical trials.]

How many of your children have FXS?

How many of them have participated in a clinical trial?

For how many of your children have you considered clinical trials?

How many times have you considered enrolling each son in a trial (go through each child individually so I can keep track please)?

Do any of your adult relatives have Fragile X syndrome?

Does anyone in your family have FXTAS?

APPENDIX F: INTERVIEW GUIDE

Child Symptomatology

What do you consider the most challenging or hardest aspects of your child's FXS?
What do you consider the most beneficial or best aspects of your child's FXS?
How do your child's FXS symptoms compare with other children you know with FXS?

Overall Parenting Experience

When did you first realize FXS was in your family?
When did you first learn that your son (or daughter) had FXS?
Can you recall what your responses were to learning the information?
What thoughts did you remember having about it then?
What feelings did you remember having about it then?
How did these thoughts and feelings change over time?
What has been challenging about being a parent of someone with FXS?
What has been beneficial or good about being a parent of someone with FXS?
If someone you knew just found out their son had FXS, what would you want them to know?

Trial Experience

Perhaps you have considered clinical trial participation for your son more than once. Or maybe you have had more than one of your sons involved in clinical trials for FXS. For this interview, I will ask you to focus on one time when you considered enrolling your son in a clinical trial for FXS. Please pick the time when you were considering having your son participate in a clinical trial for FXS that stands out most to you in some way, had the greatest impact on you, or perhaps was the most challenging.

Tell me a little about the trial decision you made this time. What made it have a big impact on you?
For this trial decision, how old is your son with FXS for whom you were considering clinical trial participation?
How old was he back when you were deciding about having him involved in a clinical trial?
How many clinical trials has your nuclear family participated in related to FXS?
How many clinical trials has your nuclear family participated in related to FXTAS?
What phase was the FXS trial that we are focusing on for this interview?
What do you think about the phase?
What do you feel about the phase?
What do you think is (or was) the purpose of the clinical trial?
What do (or did) you think researchers and doctors thought the drug might do?
What do (or did) you think the drug might do?
What do (or did) you think were the risks of being in the trial?
What did you think it would mean for your family if the trial was successful?

What did you think it would mean for your son if the trial was successful?

[Prompts for those whose trial was terminated]
What was it like when the trial ended? How did you learn the trial was ending?

Decision Making

Tell me the story of how you first learned there were drug development clinical trials for FXS.
For the clinical trial decision that we are focusing on for this interview, was there only one trial you were deciding about, or were you selecting from several options?
What has it been like (or how was it) to make a decision about having your child in the clinical trial?
What is (or was) your decision-making process like?
Who, if anyone, helped you make the decision?
What role did your child's doctor have in your decision-making process?
What role did family or friends have in your decision-making process?
What role did your son with FXS have in the decision-making process?
What are aspects of the trial that are leading you (or lead you) towards (or away from) participating?
What is influencing you (or influenced you) to participate (or not participate)?
What are aspects of the trial that you did (or do) not like?

I'm going to ask you to think about two different things. One is what you expected or actually thought would happen from the trial, the other is your hopes or what you wished or wanted to happen from the trial.
Starting with what you actually thought would happen from the trial- what expectations do you (or did you) have for the trial?
What hopes do you (or did you) have for the trial?
What motivates you (or motivated you) to participate (or not participate)?

Decisional Conflict or Regret

Some decisions are relatively easy to make and others are much harder – how easy or difficult was it for you to make the decision?
What made it easy or difficult?
How unsure were you about the decision (or how unsure are you)?
How clear did (or does) the best choice seem?
How aware of your choices do (or did) you feel?
How aware do (or did) you feel about the benefits and risks of the trial?
Do you feel you made (or are leaning towards) the right decision?
Why or why not?
Do you feel satisfied about your decision making process (or your decision)?
Why or why not?

Ending the interview

If you were giving advice to another parent of a son with FXS who is deciding about participating in a clinical trial, what would you say?

APPENDIX G: INTERVIEW SUMMARY FORM

Participant ID Number: _____

Participant type: Group 1 Group 2 Group 3

Description of Group Fit

Date of Interview: _____

Interview Start Time: _____

Interview End Time: _____

Context of Interview (setting, mood, unique situations)

Difficult parts?

Interview Question(s) Most Responsive To:

Interview Question(s) Least Responsive To:

Overall Impression of Participant's Psychological State:

Overall Impression of Interview:

Categories of Major Themes in Interview:

New or Different Information (From Previous Interviews):

Suggestions For Subsequent Interviews:

APPENDIX H: CODEBOOK – CONTEXT

CONTEXT

- Advocacy in child's care
- Age of child
    - Adult
    - Child
    - Infant
- Attitudes about research
    - Altruism
    - Endorsing or positive
    - Skeptical or negative
- Attitudes about medications
    - Skeptical or negative
    - Endorsing or positive
- Child needs
    - Academics
    - Anxiety
    - Attention
    - Behavior
    - Cognition
    - Developmental Delays
    - Language
    - Motor Skills
    - Socialization
    - Vocation or Independence
- FXS & Personhood
    - A person, not a disability
    - Affectionate and loving
    - Determination
    - Forever child
    - Happy
    - In the moment
    - Kindness and empathy
    - Nothing beneficial about FXS
    - Sense of humor
    - Intelligence
    - Smile
    - Social skills
- Symptomatology
    - Autism
    - High Functioning / Mildly affected
    - Moderately Functioning / Moderately affected
    - Low Functioning / Severely affected
        - Nonverbal
    - Seizures
- Trial Exposure

APPENDIX I: CODEBOOK - CURE

CURE

- Anticipating a cure
- Cure vs. Treatment
- Not anticipating a cure
- Likelihood of a cure child could benefit from

APPENDIX J: CODEBOOK – DECISIONAL FACTORS

DECISIONAL FACTORS AND PROCESS

- Ability to exit trial
- Coerciveness
- Drug access
    - Access post trial
    - Access without trial
- Drug mechanism
- Expectations
    - Access to drug post trial
    - Contribute to science
    - Improvement in learning ability
    - Improvement in anxiety
    - Improvement in behavior
    - Improvement in cognition
    - Improvement in focus & attention
    - Improvement in language
    - No expectations
    - The drug would not work
    - Organized trial participation process
    - Placebo effect
    - Receive results
    - Side effects
    - To be able to perceive efficacy or placebo status
    - Vague positive effect
- Hopes
    - Improvement in academics
    - Improvement in anxiety
    - Improvement in attention or focus
    - Improvement in behavior
    - Improvement in cognition
    - Cure
    - Improvement in education and learning
    - Improvement in functioning
    - Improvement in ability to form friendships
    - Improvement in child's general quality of life
    - Ultimate reduction in overall medication use
    - Improvement in speech
    - To lead to approval of drug
    - Non-specific improvement in some FXS symptom(s)
- Inconvenience
    - Blood draws
    - MRI
    - Number of appointments
    - Scheduling appointments

    - Taking time off work
    - Travel to the trial site
- Jadedness
- Making an informed decision
- Motivation
    - To decline
    - To enroll or consider enrolling
- Phase
    - No understanding of phase
    - Phase related to age range of participants
    - Phase related to disease status of participants
    - Phase related to demonstrating efficacy
    - Phase related to placebo
    - Phase related to FDA approval and access to drug
    - Phase related to safety
- Placebo
- Purpose of trial
    - Improvement in all FXS symptoms and develop a cure
    - Improvement in anxiety
    - Improvement in attention and focus
    - Improvement in behavior
    - Improvement in cognition
    - Collect data and move science forward
    - Demonstrate efficacy
    - Interact with disease mechanism
    - Improvement of language and communication
    - Improvement in education and learning
    - Match between purpose and child needs
    - Demonstrate safety
    - Improvement in social skills
- Ability to remain on regular medications
- Risk
    - Exacerbate a FX symptom
    - Lose access to the trial drug
    - No risks
    - Risk of altering child's life or personhood
    - Risk of getting a placebo
    - Risk of burden and inconvenience
    - Risk of side effects
        - Child's inability to communicate side effects
    - Risk of stopping regular medications
    - Risk that the drug will do nothing beneficial
- Risk versus benefits analysis of trial decision
- Roles in decision
    - Role of child in trial decision
        - No role

    - Role of friends and family in trial decision
        - Other than spouse, no role
    - Role of physician
        - No role
    - Role of researcher in decision
    - Physician-researcher
- Trust

APPENDIX K: CODEBOOK – TRIAL RESULTS AND EXPERIENCES

TRIAL RESULTS AND EXPERIENCES

- Advocacy for child in clinical trial context
- Betrayal
- Decisional conflict
    - High
    - Low
    - Middle
- Decisional regret
- Drug company
    - Alcobra
    - Neurin
    - Novartis
    - Seaside
- Drug Name
    - Arbaclofen
    - Lovastatin
    - MDX
    - Baclofen
    - Minocycline
    - Sertraline
    - STX209
    - AFQ
- Effect of drug on personhood
- Results and outcomes of trial
    - Access to results post trial
    - Indirect positive results
    - Issues with outcome measurements
    - Negative effects
    - No direct results on FXS symptoms
    - Positive direct results on FXS symptoms
    - Terminated trial
- Trial decision
    - Current decider
    - Decliner
    - Participator

LITERATURE CITED

Abbeduto, Leonard, Mailick Seltzer, Marsha, and Shattuck, Paul. (2004). Psychological Well-Being and Coping in Mothers of Youths With Autism, Down Syndrome, or Fragile X Syndrome. *American Journal of Mental Retardation, 109*(3), 237-254.

Abhyankar, Purva, Velikova, Galina, Summers, Barbara & Bekker, Hilary L. (2016). Identifying components in consent information needed to support informed decision making about trial participation: An interview study with women managing cancer. *Social Science & Medicine, 161,* 83-91.

Ajzen, Icek. (1991). The Theory of Planned Behavior. *Organizational Behavior and Human Decision Processes, 50,* 179-211.

American Psychological Association (2017). Personality. Retrieved from: http://www.apa.org/topics/personality/ on January 12th, 2017.

Arigo, D., Suls, J. M., & Smyth, J. M. (2014). Social Comparisons and Chronic Illness: Research Synthesis and Clinical Implications. *Health Psychology Review, 8*(2), 154-214.

Bailey, D. B., Raspa, M., Olmsted, M., & Holiday, D. B. (2008). Co-occurring conditions associated with *FMR1* gene variations: Findings from a national parent survey. *American Journal of Medical Genetics. Part A,* (146A), 2060-2069.

Bailey, Donald B., Raspa, Melissa, Wheeler, Anne, Edwards, Anne, Bishop, Ellen, Bann, Carla, Borasky, David, and Appelbaum, Paul S. (2014). Parent Ratings of Ability to Consent for Clinical Trials in Fragile X Syndrome. *Journal of Empirical Research on Human Research Ethics, 9*(3), 18-28.

Baker B. L., Blacher J. & Olsson M. B. (2005) Preschool children with and without developmental delay: behavioral problems, parents' optimism and well being. *Journal of Intellectual Disability Research, 49,* 575–590.

Barakat L, Patterson C, Mondestin V, Chavez V, Austin T, Robinson M, Li, Y, Smith-Whitley K, Cohen R. (2013). Initial development of a questionnaire evaluating perceived benefits and barriers to pediatric clinical trials participation. *Contemporary Clinical trials, 34,* 218-226.

Blacher J., Neece C. & Packowski E. (2005) Families and intellectual disability. *Current Opinion in Psychiatry, 18*, 507–513.

Bear, M. F., Huber, K. M. & Warren, S. T. (2004) The mGluR theory of fragile X mental retardation. *Trends in Neuroscience* (27), 370-377.

Belmonte M.K., & Bourgeron T. (2006). Fragile X syndrome and autism at the intersection of genetic and neural networks. *Nature Neuroscience* (10), 1221-1225.

Biedrzycki, Barbara. (2011). Factors and Outcomes of Decision Making for Cancer Clinical Trial Participation. *Oncology Nursing Forum,* 38(5), 542-552.

Blacher J. & Baker B. L. (2007) Positive impact of intellectual disability on families. *American Journal on Mental Retardation, 114,* 330–348.

Brinkley, J., Abramson, R. K., Hall, A., Wright, H. H., Gabriels, R., Gilbert, J. R., et al. (2007). Factor analysis of the aberrant behavior checklist in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 37,* 1949–1959.

Brown, E. C., Aman, M. G., & Havercamp, S. M. (2002). Factor analysis and norms for parent ratings on the Aberrant Behavior Checklist-Community for young people in special education. *Research in Developmental Disabilities*, 23, 45–60.

Chang, A. (2008). An Exploratory Survey of Nurses' Perceptions of Phase 1 Clinical Trials in Pediatric Oncology. *Association of Pediatric Hematology/Oncology Nurses, 25*(1), 14-23

Charles C, Gafni A, Whelan T. (1999). Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. *Social Science & Medicine, 49*, 651-661.

ClinicalTrials.gov Retrieved from https://www.clinicaltrials.gov/ct2/results?term=fragile+x

DeVries MC, Houtlosser M, Wit JM, *et al.* (2011). Ethical issues at the interface of clinical care and research practice in pediatric oncology: A narrative review of parents' and physicians' experiences. *BMC Med Ethics, 12*, 18.

Diefenbach & Leventhal. (1996). The Common-Sense Model of Illness Representation: Theoretical and Practical Considerations. *Journal of Social Distress and the Homeless, 5, 1,* 11-38.

Dufault, K., & Martocchio, B. C. (1985). Hope – Its Spheres and Dimensions. *Nursing Clinics of North America, 20*(2), 379-391.

Emerson E., McCulloch A., Graham H., Blacher J., Llewellyn G. & Hatton C. (2010) The mental health of parents of young children with and without developmental delays. *American Journal on Intellectual and Developmental Disability, 115,* 30–42.

Epstein RM, Street RL, Jr. Patient-Centered Communication in Cancer Care: Promoting Healing and Reducing Suffering. National Cancer Institute, NIH Publication No. 07-6225. Bethesda, MD, 2007.

Esbensen A. J., Bishop S., Seltzer M. M., Greenberg J. S. & Taylor J. L. (2010). Comparisons between individuals with autism spectrum disorders and individuals with down syndrome

in adulthood. *American Journal on Intellectual and Developmental Disabilities, 115,* 277–290.

Families Special Interest Group of IASSIDD. (2014). Families Supporting a Child with Intellectual or Developmental Disabilities: The Current State of Knowledge. *Journal of Applied Research in Intellectual Disabilities,* 27, 420-430.

Ferrer, R. A., Stanley, J. T., Graff, K., Klein W. M. P., Goodman, N., Nelson W. L. & Salazar, S. (2016). The Effect of Emotion on Visual Attention to Information and Decision Making in the Context of Informed Consent Process for Clinical Trials. *Journal of Behavioral Decision Making, 29,* 245-253.

Gerstein E. D., Crnic K. A., Blacher J. & Baker B. L. (2009). Resilience and the course of daily parenting stress in families of young children with intellectual disabilities. *Journal of Intellectual Disability Research, 53,* 981–997.

Glidden L. M. (2012). Family well-being and children with intellectual disability. In: The Oxford Handbook of Intellectual Disability and Development (eds Burack J. A., Hodapp R. M., Iarocci G. & Zigler E.), pp. 303–317. Oxford University, Oxford, UK.

Glidden L. M. & Jobe B. (2006). The longitudinal course of depression in adoptive and birth mothers of children with Intellectual disabilities. *Journal of Policy and Practice in Intellectual Disabilities, 3,* 139–142.

Glidden L. M. & Schoolcraft S. A. (2003) Depression: its trajectory and correlates in mothers rearing children with intellectual disability. *Journal of Intellectual Disability Research, 47,* 250–263.

Gomez-Mancilla, B., Berry-Kravis, E., Hagerman, R., von Raison, F., Apostol, G., Ufer, M., Gasparini, F., & Jacquemont S. (2014). Development of mavoglurant and its potential for the treatment of fragile X syndrome. *Expert Opinion Investigative Drugs* (23), 125-134.

Green S. E. (2007) "We're tired, not sad": benefits and burdens of mothering a child with a disability. *Social Science & Medicine, 64,* 150–163.

Hagerman, P. J. (2008). The fragile X prevalence paradox. *Journal of Medical Genetics* (45), 489-499.

Hagerman RJ, Berry-Kravis E, Kaufmann WE, Ono MY, Tartaglia N, Lachiewicz A, Kronk R, Delahunty C, Hessl D, Visootsak J, Picker J, Gane L, Tranfaglia M. (2009). Advances in the treatment of fragile X syndrome. *Pediatrics*, *123,* 378–390.

Hartley, Sigan L., Malick Seltzer, Marsha, Head, Lara, and Abbeduto, Leonard. (2012). Psychological Well-being in Fathers of Adolescents and Young Adults with Down Syndrome, Fragile X Syndrome, and Autism. *Family Relations, 61,* 327-342.

Hastings R. P. & Taunt H. M. (2002) Positive perception in families of children with developmental disabilities. *American Journal on Mental Retardation, 107*, 116–127.

Hatton DD, Hooper SR, Bailey DB, Skinner M, Sullivan K, Wheeler A. (2002). Problem behavior in boys with fragile X syndrome. *Am J Med Genet, 108*, 105–116.

Hoberman A, Shaikh N, Bhatnagar S, Haralam, M, Kearney D, Colborn, K, Kienholz, M, et al. (2013). Factors That Influence Parental Decisions to Participate in Clinical Research. Consenters vs Nonconsenters. *JAMA Pediatrics, 167*(6), 561-566.

Hutchinson, S. A., Wilson, M. E., Wilson, H. S. (1994). Benefits of participating in research interviews. *Journal of Nursing Scholarship, 26*(2), 161-164.

Jacquemont, Sebastien, Berry-Kravis, Elizabeth, Hagerman, Randi, von Raison, Florian, Gasparini, Fabrizio, Apostol, George, Ufer, Mike, Des Portes, Vincent, Gomez-Mancilla, Baltazar. (2014). The challenges of clinical trials in fragile X syndrome. *Psychopharmacology, 213,* 1237-1250.

James, Cynthia (2003). *How does the mode of inheritance of a genetic condition influence families?* (Doctoral Dissertation). Retrieved from ProQuest Dissertations Publishing (3080687)

Jansen LA. (2011). Two concepts of therapeutic optimism. *J Med Ethics, 37,* 563-66.

Kausar S., Jeven R. F. & Sobsey D. (2003) Hope in families of children with developmental disabilities. *Journal on Developmental Disabilities, 10*, 35–46.

Lewis, P., Abbeduto, L., Murphy, M., Richmond, E., Giles, N., Bruno, L., Schroeder, S., Anderson, J., and Orsmond, G. (2006). Psychological well-being of mothers of youth with fragile X syndrome: syndrome specificity and within-syndrome variability. *Journal of Intellectual Disability Research, 50*(12), 894-904.

Lozano, R., Hare, E. B., & Hagerman, R. J. (2014). Modulation of the GABAergic pathway for the treatment of fragile X syndrome. *Neuropsychiatric Disease and Treatment* (10), 1769-1779.

MacDonald E. E., Hastings R. P. & Fitzsimons E. (2010) Psychological acceptance mediates the impact of the behaviour problems of children with intellectual disability on fathers' psychological adjustment. *Journal of Applied Research in Intellectual Disabilities, 23,* 27–37.

MacDonald E. E., Hastings R. P. & Fitzsimons E. (2010) Psychological acceptance mediates the impact of the behaviour problems of children with intellectual disability on fathers' psychological adjustment. *Journal of Applied Research in Intellectual Disabilities, 23,* 27–37.

Markward, Martha J., Benner, Kalea, Freese, Rebekah. (2013). Perspectives of parents of making decisions about the care and treatment of a child with cancer: A review of literature. *Families, Systems & Health, 31*(4), 406-413.

Miller FG, Rosenstein DL. (2003). The therapeutic orientation to clinical trials. *New England Journal of Medicine, 348*, 1383-86.

Miodrag N. & Hodapp R. (2010) Chronic stress and health among parents of children with intellectual and developmental disabilities. *Current Opinion in Psychiatry, 23,* 407–411.

Nalavany B. A., Glidden L. M. & Ryan S. D. (2009) Parental satisfaction in the adoption of children with learning disorders: the role of behavior problems. *Family Relations, 58,* 621–633.

Olsson M. B. & Hwang C. P. (2001) Depression in mothers and fathers of children with intellectual disability. *Journal of Intellectual Disability Research* 45, 535–543.

Olsson M. B., Larsman P. & Hwang C. P. (2008) The relation between risk, sense of coherence and well-being in parents of children with and without intellectual disabilities. *Journal of Policy and Practice in Intellectual Disability, 5,* 227–236.

Peay, H. L., Tibben, A., Fisher, T., Brenna, E., & Biesecker, B. B. (2014). Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy. *Clinical Trials* (11), 77-85.

Perez, M. M. B., Menear, M., Brehaut, J. C., & Legare, F. (2016). Extent and Predictors of Decision Regret about Health Care Decisions: A Systematic Review. *Medical Decision Making* (36), 777-790.

Raspa, Melissa, Bailey, Donald B., Bann, Carla, and Bishop, Ellen. (2014). Modeling Family Adaptation to Fragile X Syndrome. *American Journal on Intellectual and Developmental Disabilities, 119*(1), 33-48.

Saloviita T., Italinna M. & Leinonen E. (2003) Explaining the parental stress of fathers and mothers caring for a child with intellectual disability: a double ABCX model. *Journal of Intellectual Disability Research, 47,* 300–312.

Sansone SM, Widaman KF, Hall SS, Reiss AL, Lightbody A, Kaufmann WE, Berry-Kravis E, Lachiewicz A, Brown EC, Hessl D. 2012. Psychometric study of the Aberrant Behavior Checklist in fragile X syndrome and implications for targeted treatment. *J Autism Dev Disord, 42*, 1377–1392.

Scorgie K. & Sobsey D. (2000) Transformational outcomes associated with parenting children who have disabilities. *Mental Retardation, 38*, 195–206.

Shilling V, and Young, B. (2009). How do parents experience being asked to enter a child in a randomized controlled trial? *BMC Med Ethics, 10,* 1.

Singer G. H. S. (2006). Meta-analysis of comparative studies of depression in mothers of children with and without developmental disabilities. *American Journal on Mental Retardation, 111,* 155–169.

Snethen, J. A., Broome, M. E., Knafl, K., Deatrick J.A., & Angst, D. B. (2006). Family Patterns of Decision-Making in Pediatric Clinical Trials. *Research in Nursing and Health, 29,* 223-232.

Symons FJ, Byiers BJ, Raspa M, Bishop E, Bailey DB. (2010). Self-injurious behavior and fragile X syndrome: findings from the National Fragile X Survey. *Am J Intellect Dev Disabil, 115,* 473–481.

Thompson, Andrew, and Sunol, Rosa. (1995). Expectations as Determinants of Patient Satisfaction: Concepts, Theory, and Evidence. *International Journal for Quality in Health Care, 7*(2), 127-141.

Totsika V., Hastings R. P., Emerson E., Berridge D. M. & Lancaster G. A. (2011a) Behavior problems at five years of age and maternal mental health in autism and intellectual disability. *Journal of Abnormal Child Psychology, 39,* 1137–1147.

Totsika V., Hastings R. P., Emerson E., Lancaster G. A. & Berridge D. M. (2011b) A population-based investigation of behavioural and emotional problems and maternal mental health: associations with autism spectrum disorder and intellectual disability. *Journal of Child Psychology & Psychiatry and Allied Disciplines, 52,* 91–99.

U.S. Food and Drug Administration (FDA). (2015). Step 3: Clinical Research. Retrieved from: http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm on October 6th, 2015.

Vaismoradi M, Turunen H, Bondas T. (2013). Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nursing and Health Sciences, 15,* 398-405.

Vanhelst J, Hardy L, Bert D, Duhem S, Coopman S, Libersa C, Deplanque D, Gottrand F, Beghin L. (2013). Effect of child health status on parents' allowing children to participate in pediatric research. *BMC Medical Ethics, 14*(7).

Wang, Lan-Hsiang, Tsai, Yun-Fang, Chen, Jen-Shi, and Tsay, Pei-Kwei. (2011). Intention, Needs, and Expectations of Cancer Patients Participating in Clinical Trials. *Cancer Nursing, 34*(2), 117-123.

Wenzel. Jennifer A., Mbah, Olive, Xu, Jiayun, Moscou-Jackson, Gyasi, Saleem, Haneefa, Sakyi Kwame, & Ford, Jean G. (2015). A Model of Cancer Clinical Trial Decision-

making Informed by African-American Cancer Patients. *Journal of Racial and Ethnic Health Disparities, 2*(2), 192-199.

Wheeler, Anne, Raspa, Melissa, Bann, Carla, Bishop, Ellen, Hessl, David, Sacco, Pat, and Bailey, Donald B. (2013). Anxiety, Attention Problems, Hyperactivity, and the Aberrant Behavior Checklist in Fragile X Syndrome. *American Journal of Medical Genetics Part A* (164A), 141-155.

Ylven R., Bjorck-Akesson E. & Grandlund G. M. (2006) Literature review of positive functioning in families with children with a disability. *Journal of Policy and Practice in Intellectual Disabilities, 3,* 253–270

CURRICULUM VITAE

Celeste D'Amanda

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Education

ScM. **The Johns Hopkins University / The National Human Genome Institute.** *Expected Graduation May 2017*. Thesis Topic: Fragile X Syndrome Clinical Trials: Hope, Expectations, and Decision Making of Parents.

B.A. **Bennington College.** Concentration (Major): Biology and Chemistry. Overall GPA: 3.85.

Genetic Counseling Graduate Training

- **National Institute of Neurological Disorders and Stroke.** Worked with patients in neurology clinic. — Fall 2016
- **Georgetown Lombardi Comprehensive Cancer Center.** Worked with patients in oncology clinic. — Fall 2016
- **GeneDx.** Gained exposure to genetic testing laboratory proceedings and contributed to research related to copy number variations in genes associated with cardiac arrhythmia. — Summer 2016
- **The Johns Hopkins Hospital, Pediatric & Adult Specialty Clinics**. Counseled in general genetics, connective tissue, skeletal dysplasia, and epigenetics clinics. — Spring 2016
- **National Eye Institute.** Counseled in ophthalmic genetics visual function branch clinic under NIH research protocols. — Summer-Fall 2016, Fall-Winter 2015
- **Undiagnosed Diseases Program.** Counseled patients seeking a diagnosis at the NIH. — Fall 2016 and Fall 2015
- **Kennedy Krieger Institute.** Counseled families in the neurogenetics, neuromuscular, and preschool interdisciplinary clinics. Created a patient information sheet on chromosome microarray testing. — Summer 2015
- **Greater Baltimore Medical Center.** Worked with patients in prenatal and pediatric clinics. — Spring 2015
- **Genetic and Rare Diseases Information Center.** Assisted with responses to public requests for information. Completed an original project related to the treatment of requests from international inquirers. — Fall 2014

Past Lab & Research Experience

- **Lab Assistant, Bennington College**. Worked in the laboratory of Dr. Amie McClellan on preparing experimental materials for the Introduction to Cell Biology course. — Spring 2013

- **Lab Assistant, UMass Medical School.** Worked in the laboratory of Dr. Hardy Kornfeld on projects related to diabetes and tuberculosis. Gained familiarity with animal model (mouse) research procedures, qPCR, and cell culturing. — Winter 2012
- **Lab Assistant, City College of NY.** Interned in the laboratory of Dr. Avrom Caplan. Worked on a yeast project related to protein aggregation. — Winter 2011

Volunteer Experience

- **Ulman Cancer Fund for Young Adults.** Assisting with fund raising campaigns for support services targeted at young adults with cancer. — Spring 2016 - Present
- **United States Science and Engineering Festival.** Interacted with the public representing NHGRI. — Spring 2016
- **Parent Project Muscular Dystrophy.** Performed phone interviews with DMD carriers about their perceived health risks. — Fall 2014
- **Isaiah House**. Acted as a volunteer hospice caregiver in bereavement counseling. Provided emotional and physical support to the dying and their families. — Feb-July 2014
- **Sexual Assault Crisis Center of Eastern Connecticut.** Received 30 hours of training to become a certified sexual assault crisis counselor in the State of Connecticut. — Fall 2013
- **Urban Choice Charter School.** Teaching assistant for a fourth grade classroom. Provided one-on-one tutoring of students struggling in math, reading, and writing. — Winter 2010
- **Isaiah House.** Worked with the dying in providing emotional and physical support. Provided company to patients. — September 2008-June 2009
- **Harley School Hospice Program**. Participated in training program for hospice volunteer work. — September 2007-June 2009

Professional Presentations

- Clinician Compassion Fatigue and Burnout (Post-Clinic Conference, NHGRI) — Spring 2015
- International Inquiries at GARD — Spring 2015
- Disclosure of Vision Loss (Post-Clinic Conference, NHGRI) — Fall 2016
- Fragile X Syndrome: Hope, Expectations, and Decision Making of Parents (NHGRI Research Symposium Poster Session) — Fall 2016

Specific Skills

- Research with databases: OMIM, ClinVar, HGMD, GeneReviews,

GeneTests, PubMed, EBSCO, Web of Science, University of Miami Genomic Oligoarray and SNP array evaluation tool V2.0, and others.

- Variant interpretation with databases: ExAC, NHLBI exome, PubMed, HGMD, Mutation Taster.
- Cancer modeling software: Gail, CancerGene, Tyrer-Cuzick.
- Computer: MacOX/Windows, Microsoft Excel, Word, Outlook, PowerPoint, and Google software suits.

Memberships and Honors

- National Society of Genetic Counselors, Student Member — 2015 - Present
- Bennington College Judith Schneider '61 Scholarship. Awarded annually to an outstanding science or math student. — 2012

Interests

- Qualitative research methods in social and behavioral sciences
- Treatment development clinical trial decision making and informed consent processes
- Patient care and advocacy
- Palliative and end of life care